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# Karyotype, Meiosis and Spermatogenesis in a Sample of Men Attending an Infertility Clinic

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# Karyotype, Meiosis and Spermatogenesis in a Sample of Men Attending an Infertility Clinic

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# PREFACE

This investigation was carried out at the Institute for Medical Genetics and at the Department of Obstetrics and Gynaecology, both of the University of Uppsala, Sweden.

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This investigation is part of a research programme on 'Clinical Cytogenetics, Human Chromosomes and Gene Markers' under the direction of Professor JAN A. BÖÖK, M.D., Ph.D., at the Institute for Medical Genetics in Uppsala, supported by grants from the Swedish Medical Research Council (No. 19X-244) and the US National Institutes of Health of the US Public Health Service (grant No. NB-4320). During 1963/64 I held a postgraduate fellowship of a training programme in medical genetics, supported by the US National Institutes of Health (training grant No. 5T1 GM-355 to Professor JAN A. BÖÖK). I have received additional support for this work through grants from the Medical Faculty of the University of Uppsala, the 'Prenatal Research Fund' of the Stockholm newspaper 'Expressen', the Swedish Society for Medical Research, the 'Alice Karlsson Memorial Fund' and the 'Kristiane and O. F. Hedström Memorial Fund'.

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# INTRODUCTION

Human fertility has an extremely complex background which is dependent on individual constitution, environment, motivation and performance. This complexity is further increased by the fact that these factors must be related to both individuals in a partnership. Fertility requires the production of functioning gametes in both sexes and barren marriages are as often due to the male as the female partner. The seminal characteristics, judged by the number and morphology of gametes and their functional capacity as well as physiological and biochemical properties of seminal fluid are known to be of great importance to male fertility.

When they are not caused by transient environmental influences; gametogenetic deficiences are very often long-standing and subject to only small variations. With very few exceptions, therapeutic attempts to improve gametogenesis have as yet been unsuccessful.

In this work the inquiry was limited to one important cause of variations in fertility namely individual genetical differences depending particularly on chromosomal aberrations and their relation to spermatogenesis in the human male. In principle, deviations from the normal karyotype may affect individual fertility in a number of ways. Firstly the abnormal karyotype may cause a pathological condition in its carrier, which secondarily eliminates or reduces the fertility potential (examples are Downs syndrome, sex chromosome variations causing abnormalities of sexual development and endocrine dysfunction). Secondly, the abnormal karyotype, which may also have no negative effect on its carrier, may include chromosomes which make meiosis irregular with a substantial reduction of the number of gametes produced. A similar abnormal karyotype may lead to the production of gametes which are heteroploid or carry structurally rearranged chromosomes, but which still retain their capacity to fertilize an ovum. In such cases, a certain proportion of the zygotes may develop abnormally or not at all.

A systematical investigation on the reproductive capacity of an individual and its correlation to genetical conditions requires some basic

definitions. The fecundity of an individual is thus defined, in this work, as the ability to produce functioning gametes whereas fertility is taken to mean the measurable ability to produce progeny in terms of live births, still births and abortions.

With techniques presently available, analysis of fecundity is limited in practice to the male sex of mammals and man.

# PREVIOUS INVESTIGATIONS

The genetical aspects of human infertility were reviewed by PENROSE (1963) who stated that genic factors as well as chromosomal aberrations may give rise to lethal conditions or essentially infertile types with a consequent reduction in the total sum of surviving offspring as the result.

Lethal conditions, such as zygotic lethality, have been described in mammals by SNELL *et al.* (1934), SNELL and PICKEN (1935), HERTWIG (1935, 1938 and 1940) and BRENNEKE (1937).

A series of 200 spontaneous abortions was examined by CARR (1965) who found that 44 of them had abnormal karyotypes. Several investigators *e.g.*, SCHMID and HATFIELD (1962), VISLIE *et al.* (1962), LEJEUNE *et al.* (1964) have suggested unbalanced karyotypes as a cause of spontaneous miscarriages in families where one parent proves to be a translocation heterozygote. While certain genetical factors act directly on the reproductive system or exert their effect by elimination of zygotes, infertility in man is often indirectly associated with other genetical determinants. Many individuals are made effectively infertile because of genetically determined physical or mental defects which more or less exclude them from normal heterosexual relationships. However, exceptions are known, as in Downs syndrome with trisomy–21 where fertile females have been described (FORSSMAN *et al.* 1961, THULINE and PRIEST 1961, THOMPSON 1961 and PRIEST *et al.* 1963). By contrast paternity in males with Downs syndrome has not been reported.

The whole gametogenetic process in the male gonad is referred to as spermatogenesis. The most immature type of germ cells in the seminiferous tubules are the spermatogonia which divide mitotically to produce primary spermatocytes. Following the first meiotic division, the diploid first spermatocyte yields 2 haploid secondary spermatocytes which undergo a second meiotic division, yielding 2 spermatids. The subsequent maturation process, during which the spermatids undergo differentiation into mature gametes, is referred to as spermiogenesis. In the very early embryo, primordial germ cells are located in the lining

of the yolk sac and hindgut. Later they move to the gonadal ridges to become enclosed in the sex cords (see review by ROOSEN-RUNGE 1964). Factors which interfere with this migration are known to have severe consequences on the subsequent production of sperms in the adult individual. In mice, the original number of primordial germ cells and their efficiency of migration were shown, by MINZ (1960a and b), to be controlled by genes. A similar mechanism has been suggested as the cause of the germinal cell aplasia syndrome in the human male (del CASTILLO *et al.* 1947). There are several examples which show that the intratubular gametogenetic process is controlled by special genes. Gene mutations can cause spermatogenetic depression or arrest at different levels as well as changes of sperm morphology.

Such intratubular spermatogenetic arrest was shown to be caused by gene mutations in the african mouse, Mastomys, by MENZIES (1957), in guinea pigs by SINKS (1955), JAKWAY and YOUNG (1958) and in the ruby eyed male hamster, Mesocricetus aureatus, by BRUCE (1958). The same phenomenon was observed in male mice subsequent to the administration of a chemical mutagen, triethylenemelamine (CATTANACH 1957, CATTANACH and EDWARDS 1958) and by HOLLANDER *et al.* (1960) following X-ray irradiation.

A change of sperm morphology caused by gene mutation was reported by HANCOCK (1949) in 7 related Friesian bulls with an inherited acrosomal defect of their sperm heads causing loss of reproductive function. A similar condition was described in the house mouse by RAJASEKARASETTY (1954).

NOWAKOWSKI and LENZ (1961) reviewed the genetical aspects of male hypogonadism. With respect to man, however, few data have been reported on genetic factors and impaired fecundity.

Abnormal distribution of the chromosomes at mitotic as well as meiotic anaphases will produce genetically unbalanced daughter cells. The genetic constitution of such unbalanced cells may sometimes be incompatible with further life and propagation of that cell type. Other unbalanced cells may, however, be viable and permit further propagation. Divisional errors during meiosis may produce unbalanced gametes. Gametes of this type are known to be viable (FORD 1961) and capable of fertilizing an ovum (FRØLAND *et al.* 1963a, LEJEUNE *et al.* 1964). Sex chromosome aberrations are the most common type found in man (COURT-BROWN *et al.* 1964a and POLANI 1964).

In human males, the first evidence of an association between chromosome aberrations and fertility was obtained when some of the infertile

individuals with Klinefelter's syndrome were shown to be sex chromatin positive by PLUNKETT and BARR (1956) and BRADBURY *et al.* (1956). This discovery was followed by the demonstration of JACOBS and STRONG (1959), that sex chromatin positive males could have an XXY sex chromosome constitution. Although the XXY sex chromosome constitution is the most frequent one in sex chromatin positive males, there are several other variants, usually mosaic, who have sex chromatin bodies in their interphase nuclei (see review by COURT-BROWN *et al.* 1964a).

Histological examination of testicular biopsy specimens from chromatin positive males, however, indicated active spermatogenesis in some seminiferous tubules (BUNGE and BRADBURY 1956, JIRASEK and RABOCH 1957, FERGUSON-SMITH and MUNRO 1958). Mature sperms were occasionally observed, and the latter authors stated that 'fertility in such an individual is a possibility'. Fertility has, however, never been conclusively proven in individuals with an XXY sex chromosomal constitution although it has been demonstrated in individuals with a presumable XY/XXY mosaicism (WARBURG 1963, DOWLING and KNOX 1963, COURT-BROWN *et al.* 1964b).

Few systematical investigations on the correlation between fertility and cytogenetical conditions in subfertile human males have been reported. FERGUSON-SMITH *et al.* (1957) estimated that the incidence of sex chromatin positive men in a male subfertility clinic was between 1 and 3%. If only men with less than 1 million sperms per ml were considered, the incidence was about 11%. STEWART *et al.* (1959) claimed that patients with Klinefelter's syndrome, regardless of their karyotypes, may 'account for something like one-third of all cases of high-grade infertility in the male'.

Many chromatin negative individuals with the clinical manifestations of Klinefelter's syndrome have specific histological changes in their testicles. These were first described by del CASTILLO *et al.* (1947) and are referred to as germinal cell aplasia.

Chromosome studies on such individuals have mostly shown normal karyotypes (SOLARI *et al.* 1963; VALENCIA *et al.* 1963 and FERGUSON-SMITH *et al.* 1963). Recently, however, de la CHAPELLE *et al.* (1964, THERKELSEN (1964a and b), FRØLAND (1964, personal communication) and FERGUSON-SMITH (1965) have described individuals with a male phenotype but a normal female karyotype associated with gonadal dysgenesis and germinal cell aplasia in an only testicle.

VAN WIJK *et al.* (1962, 1963) described Y chromosomes of unusual

sizes in a sample of 29 oligospermic or aspermic males, excluding patients with Klinefelters syndrome. They found 3 individuals with unusually large Y chromosomes and 1 individual with a very small Y chromosome. MAKINO (1964) also described large Y chromosomes in association with severe oligospermia.

The causal relationship between inherited reduced fertility and segmental chromosomal interchanges was first suggested by BELLING (1925) to explain the results obtained by the same author in species crosses of Stizolobium (BELLING 1914). The assumption that a certain proportion of unbalanced gametes might be produced by abnormal segregation and distribution of structurally rearranged chromosomes during the first meiotic division was later confirmed by BURNHAM (1930, 1932, 1934), SUTTON (1935) and others. The progeny of X-ray irradiated mice was reported to be 'semi-sterile' by SNELL (1935) who suggested that reciprocal translocations had been induced in the offspring of the irradiated animals. Cytogenetical evidence in favour of this hypothesis was obtained by KOLLER and AUERBACH (1941) in translocation heterozygous mice. The semi-sterility was shown to be due to an increased fetal death (SNELL *et al.* 1934; SNELL 1935; SNELL and PICKEN 1935; HERTWIG 1935, 1938, 1940; BRENNEKE 1937). The correlation between segmental interchange and fertility in mice was investigated in detail by Koller (1944) who, in addition, found no difference of sperm motility between normal and interchange mice.

Semi-sterility due to translocation heterozygosity has also been demonstrated in a boar by HENRICSSON and BÄCKSTRÖM (1964).

Investigations on the association between structural interchanges and fecundity and fertility require an analysis of the structure and behaviour of the meiotic chromosomes of primary spermatocytes.

The first systematical investigations of the chromosomal constitution in human male germ cells was made by von WINIWARTER (1912) who tried to determine the diploid chromosome number of man in the spermatogonial divisions of cut sections. PAINTER (1923) showed that the male sex chromosome constitution was of the XY type and also described an asymmetrical sex bivalent at metaphase I. These findings were later confirmed by EWANS and SWEZY (1929), SHIWAGO and ANDRES (1932), MINOUCHI and OHTA (1933) and others. KOLLER (1937) analysed in some detail the behaviour of human sex chromosomes at metaphase I and anaphase I and suggested that during first meiotic pro- and metaphase the X and Y chromosomes were usually associated by a real chiasma. This suggestion has not as yet been confirmed (SACHS

1954; Ford and Hamerton 1956; Böök and Kjessler 1964; Sasaki and Makino 1965). According to Sachs (1954), the terminal connexion between the X and Y chromosomes observed at diakinesis and metaphase I is more likely to be a remnant structure of the sex vesicle than a real chiasma.

The structure and behaviour of the autosomes of man at diakinesis and metaphase I were first investigated by Ford and Hamerton (1956) who examined the chiasma frequency and bivalent structure of 23 cells derived from 3 men. The average chiasma frequency was found to be 55,9 chiasmata per cell with a range of 50 to 63.

Since the investigation by Ford and Hamerton (1956) was published, only a few reports have appeared on meiosis in man and a rather limited amount of new information has been added (Chu and Giles 1959; Ferguson-Smith 1961; Makino *et al.* 1962; Darlington and Haque 1962; Böök and Kjessler 1964; Sasaki 1964). Recently, Sasaki and Makino (1965) examined the meiotic chromosomes in testicular material derived from 16 Japanese men who were hospitalized for different reasons. They claimed that a 'failure of pairing' occurred in 27% of the primary spermatocytes. However, it was pointed out that these observations might have been due in part to preparation artefacts. Bivalents were observed by the same authors with 1 to 6 chiasmata each, but no frequency distribution of chiasmata was reported.

Meiotic studies have only been made in a few instances of human congenital disorders or other pathological conditions. Two human intersexes were examined by Severinghaus (1942) and Greene *et al.* (1952) but technical difficulties made the observations rather inconclusive. Mittwoch (1952), Miller *et al.* (1960) and Sasaki (1965) have analysed the meiotic chromosomes in individuals with trisomy 21 and Downs syndrome.

Hamerton *et al.* (1961) were the first to report observations on the structure and behaviour of meiotic chromosomes at diakinesis and metaphase I in a male carrier of a balanced D/G translocation. They were able to demonstrate consistent trivalent formation in primary spermatocytes, thus confirming the presumptive karyotype interpretation of a D/G translocation based on analysis of mitotic metaphases. A subfertile man with a D/D translocation and trivalent formation at meiosis with a reduced number of chromosome bodies in primary spermatocytes was briefly reported by Kjessler (1964). A third case of balanced translocation heterozygosity in a male, first mentioned by Fraccaro (1964), has been described in detail by Lindsten *et al.* (1965), who were able

to show a multivalent of varying structure at diakineses and metaphases I. POLANI (1964) also mentioned a ring shaped multivalent in a male translocation carrier.

FORD and HAMERTON (1956) suggested that analysis of meiotic chromosomes 'may also be able to assist in the causal analysis of infertility, at least in the male'.

### *Aim of the Present Investigation*

With reference to the significance of meiotic disturbances as a cause of sterility, or reduced fertility, in a multitude of organisms and the recent development in human cytogenetics, it was decided to examine such relationships in man.

For this purpose, a consecutive series of male partners in barren marriages attending an infertility clinic should have to be registered, and examined with respect to mitotic karyotype, meiosis and spermatogenesis together with relevant clinical data.

## MATERIAL

The Infertility clinic at the Department of Obstetrics and Gynaecology of the University Hospital in Uppsala admits, without regional restrictions, patients who are referred from other medical services or come on their own initiative.

All male patients who attended this clinic during the year between April, 1st 1964 and March, 31st 1965, were registered for this investigation. These numbered 178 and were almost all husbands of primarily or secondarily infertile marriages. All these men were asked for samples of blood for chromosome analyses of cultured leucocytes and also seminal fluid for serial analyses of sperm count and sperm morphology.

On September, 1st 1965, such examinations had been completed in 135 patients. The remaining 43 patients were excluded because they refused to co-operate, presented technical difficulties or were still under investigation. The series of patients to be considered here thus comprises 135 men. The results of gynaecological investigations for infertility made on their partners have not been taken into consideration.

In 47 out of the 135 patients, the karyotype determinations were supplemented by chromosome studies on cell cultures derived from testicular or skin biopsy specimens or both. Testicular biopsy was per-

formed on all men with aspermia or cryptospermia, the latter being defined as a count of less than 1 mill sperms per ml, JOHANSSON (1957). Patients with a count of more than 1 mill sperms per ml had testicular biopsies only when they volunteered. The testicular specimens obtained by biopsy provided material for direct cytological preparations for the analysis of meiotic chromosomes. When indicated, they were also used for cell cultures and for histological examination of testicular morphology.

Six of the patients claimed to have fathered children, 3 of them with their present partners, 2 with one other partner and 1 with 2 other partners.

The ages of the 135 patients ranged from 19 to 48 years with a mean of 30.5. On admission, the duration of the current period of infertility varied between 6 months and 16 years with an average of 4.4 years.

Data for individual patients have been summarized in the tables and figures of the Appendix.

A significant number of these patients were referred subsequent to examinations elsewhere. For this reason, the present series may not be a true random sample from the universe of infertile couples.

## METHODS

### *Analysis of Mitotic Chromosomes*

The karyotype of each patient was determined by analysis of mitotic metaphase chromosomes in cultured leucocytes from peripheral blood. The cultures were prepared and processed by the method described by MOOREHEAD *et al.* (1960) with minor modifications. The cytological preparations were made by the air-drying technique of ROTHFELS and SIMINOWICH (1958) and stained in Giemsa. Samples of heparinized whole blood were sometimes received by post and were therefore processed with a delay of four or five days without adverse consequences.

If required, chromosome analyses were also carried out on cell cultures derived from biopsy specimens of skin and testicular tissue or both. The cells were grown in small Carrel flasks containing a medium composed of 20% pooled human serum, 35% Parker's solution (199) and 45% Hanks' solution (balanced salt solution). 5 ml of chicken embryo extract and small amounts of buffered benzylpenicillin and dihydrostreptomycin were added to each 100 ml of this medium. The Carrel flasks were rinsed with a few ml of culture medium and small pieces of

minced tissue were dispersed over the bottom. Implantations into plasma clots were not found necessary for early onset of growth. Prior to their sealing, the atmospheric air within the flasks was replaced by expiratory air blown through a Pasteur-pipette plugged with cotton wool. The cultures were observed by means of an inverted, phase contrast microscope. When actively dividing and migrating cells appeared, the culture medium was exchanged every second day. Chromosome preparations were made from primary cultures as well as from subcultures of varying order.

By treatment with trypsin, a suspension of cells was obtained which was processed according to the same technique used for the leucocyte cultures.

Chromosome counts and preliminary karyotype analyses were carried out at a magnification of $\times 1000$. Between 10 and 242 cells were drawn and counted in each patient. At least 3 suitable cells in metaphase with the modal number of chromosomes and all cells with a non-modal chromosome count were photographed with a ZEISS Automatic photomicroscope using ADOX KB 14 film. The chromosomes were cut out from enlarged photomicrographs and matched in pairs according to the 'Denver system for classification of human mitotic chromosomes' (1960). (Fig. 1.)

Identification of chromosomal mosaicism is often difficult, and while it may be recognized it is not possible to exclude. It requires analyses of cells derived from preferably more than one tissue and these cells should show karyotypes consistently belonging to two or more cell populations. The criteria for identification of mosaicism have been reviewed in detail by HARNDEN (1964); COURT-BROWN *et al.* (1964).

Patients suspected of chromosomal mosaicism were asked to submit to skin and testicular biopsy and cells from more than one tissue were analysed in all cases but one.

### *Analysis of Meiotic Chromosomes*

Earlier investigations of spermatogenesis in man have usually been restricted to the histological analysis of testicular morphology in cut sections. Chromosomal irregularities during meiosis have been inferred from the presence of abnormal germinal cell elements in such preparations (c.f. TILLINGER, 1957).

A detailed analysis of the behaviour of the chromosomes during the different stages of meiosis is likely to contribute substantially to the understanding of gametogenesis. Analysis of the chromosomes at diakinesis and metaphase I will be useful for the detection and interpretation of karyotypes with numerical chromosome variations and structural aberrations of the translocation type.

For the detection of inversions, other stages of meiosis such as pachytene and anaphase I are preferably analysed.

A special preparation of the testicular material removed at surgical biopsy is required for good visualisation of the chromosomes during meiosis. The following technique was found satisfactory, particularly for diagnostic purposes where biopsy specimens must be quite small. Testicular biopsies were performed under light general anaesthesia, mostly according to the technique described by Nordlander (1948), and the patients were able to leave hospital after a few hours of rest. No complications occurred. A piece of tissue about $3 \times 3 \times 3$ mm is sufficient for chromosome preparations. Immediately after removal, the specimen was transferred into a hypotonic (1.12%) trisodium citrate solution. No difference in technical quality was observed when preparations were made within four hours of surgical removal.

For the first one third of the patients in this series chromosome preparations were made according to the technique described by Böök and Kjessler (1964). For the rest, the following modification was found useful.

Following hypotonic pretreatment for a minimum of 20 min the testicular biopsy specimen was cut into small pieces. These pieces were transferred to a solution of 2% natural orcein (Gurr) in 50% acetic acid. After 15 min, the pieces were handled, one at a time, as follows. They were placed on glass slides in 2 to 3 drops of the acetic orecin solution and the seminiferous tubules were gently teased with two preparation needles, one spearformed and the other flat with two sharp edges. The germinal cells were brought into suspension by a series of 'cutting-pressing-cutting' operations using mainly the flat ended and sharp edged needle. Residual tubular debris was then moved to the centre of the slide. Holding the slide at an angle of about 60°, the debris was finally moved upwards by the point of the preparation needle, while the suspension of germinal cells trickled downwards. Having removed the debris from the slide, a cover slip was applied and excess fluid removed by filter paper. The cells in the preparations were squashed by gentle pressure, repeated until a satisfactory spread of the chromosomes could

be observed in the microscope. The preparations were finally sealed with Krönigs cement. Six to ten slides were usually prepared within less than two hours from surgical biopsy.

The slides were systematically scanned for suitable cells in meiotic division. Apparently undamaged cells at diakinesis or metaphase I were selected for further analysis.

Firstly, the number of chromosome elements was determined for each of these cells. These chromosomal bodies may consist of two or more chromosomes forming bivalents or multivalents, as well as single chromosomes, *i.e.* univalents or even fragments from broken chromosomes.

The pairing of homologous chromosomes during early, first meiotic prophase is followed by a reduplication of each chromosome into two identical chromatids which, while their centromeres remain undivided, form chiasmata with their homologous partner chromatids. At points of crossing, an exchange of parts between homologous chromatids may occur through breakage and reunion. During the following stages the chiasmata usually appear more distinct due to the increasing spiralization and contraction of the chromosomes together with the pulling apart of the centromeres of homologous pairs (cf. DARLINGTON, 1931, 1937; SWANSON, 1960).

The size and form of the chromosome configurations from diakinesis through metaphase I will depend mainly on the number of associated chromosomes, their individual size, and positions of their centromeres and the number and location of chiasmata joining homologous arms. Normally, pairing and chiasma formation (crossing over) takes place between homologous chromosome segments but this process is controlled also by physical and chemical properties of the chromosomes as well as by other factors, *e.g.* single recessive gene differences etc. The usual appearance of the bivalents at diakinesis and metaphase I in primary spermatocytes of men with normal karyotypes is shown in Fig. 2.

The sex chromosomes were analysed first. Usually, they are seen as an unequal rod shaped bivalent as described by PAINTER (1923), KOLLER (1937), FORD and HAMERTON (1956), BÖÖK and KJESSLER (1964) and SASAKI and MAKINO (1965). However, they may also appear as two univalents of different size and shape. If so, the X chromosome has a rod-like appearance and the Y chromosome is seen as a small dot. The presence of the sex chromosomes as univalents may only be considered a likely interpretation when the analysis of the other chromosomal

elements in the cell proves the presence of the expected number of autosomes. Subsequently, the structure of the autosomal chromosome elements were analysed in detail in order to examine whether or not indications of structural or numerical chromosome variations could be found. As a measure of the pairing efficiency, the total number of chiasmata and the number of terminal chiasmata were determined for each bivalent or multivalent and also for each cell. Following HUSKINS and HEARNE (1936), 'each bivalent configuration was assessed as having the minimum number of chiasmata necessary for the formation of such a configuration'. Furthermore, the terminalisation coefficient was calculated for all completely analysed cells. This coefficient is defined as 'the ratio of terminal to total chiasmata in a stage at which the cell has been fixed' (SLIZYNSKI, 1955). The frequency distribution of chiasmata per bivalent was examined for each cell and individual values were calculated according to the method used in investigations on mice by CREW and KOLLER (1932) and SLIZYNSKI (1955).

### *Sperm Analyses*

For serial analyses of sperm count and sperm morphology, ejaculated seminal fluid was obtained from all men registered for this investigation.

Two independent sperm counts were made on each sample using a FUCHS-ROSENTHAL chamber and following the routine techniques for counting cells in suspension. The average value was regarded as representative for the sample analysed. Sperm morphology was examined in seminal smears made on glass slides. The smears were fixed and mounted but not stained. The sperms were examined at a magnification of $\times$ 1000 by means of a phase contrast microscope. The standards for sperm morphology were mainly adopted from VARNEK (1944) and MCLEOD (1964). A total of three hundred sperms were observed and registered with regard to the appearance of the sperm head, mid-piece and tail. The examinations were made independently by the same three observers throughout this investigation. The observers were not aware of one another's results or the identity of the patient under study. The average of the three differential cell counts was regarded as representative for the specimen analysed. Morphologically abnormal sperms were classified as such and not subgrouped further.

A variety of environmental factors such as infections, physical and mental strain, malnutrition, drugs and other agents are known to exert

an influence on spermatogenesis resulting in changes of sperm counts as well as sperm morphology (VASTERLING, 1960; LEBLOND *et al.*, 1963; MCLEOD, 1964). A certain variation of sperm count and sperm morphology normally occurs in the human male as pointed out by MCLEOD and GOLD (1956) and FREUND (1962, 1963). The analysis of a single seminal specimen is therefore inadequate for conclusions about the current sperm producing capacity. To reduce the influence of occasional environmental factors with negative effects on spermatogenesis, the sperm analyses were repeated four times. HELLER and CLERMONT (1963) estimated that the time necessary for an immature spermatogonium to develop into a mature sperm was about 64 days. This implies that the maximum interval between an environmental influence on spermatogenesis and its effect on the sperm count and sperm morphology should be about 64 days. The 4 samples of ejaculate were therefore collected with a minimum interval of 64 days between the second and the third specimens. Sexual continence for 4 to 5 days before emission was recommended. The ejaculates were collected in special glass containers provided by the laboratory.

The results of the sperm analyses have been summarized in Table A of the Appendix.

### *Histological Examination of the Testicular Morphology*

Almost all patients who had a testicular biopsy also had an examination of testicular histology. Specimens were fixed in a freshly prepared mixture of absolute ethanol and absolute methanol in equal proportions. They were subsequently processed by routine techniques and stained in haematoxylin-eosin and van Gieson. The slides were examined by means of a light microscope at a magnification of $\times$ 100 to $\times$ 1000. Observations were classified according to TILLINGER (1957).

The histological data have been summarized in Table C of the Appendix.

### *Clinical Investigations*

All patients were asked about previous conceptions as well as the duration and other relevant details concerning the current period of involuntary childlessness. The patients who agreed to testicular biopsy had a complete clinical examination and their history was supplemented

by questions about their physical, mental and sexual development as well as about their family, social and previous medical history.

The clinical observations have been summarized in Tables A and D of the Appendix.

*Fig.1.* Mitotic metaphase and corresponding karyotype of a normal male. Cultured leucocyte.

# RESULTS

## *Mitotic Karyotypes*

Karyotype determinations of the 135 men of the present sample revealed that 12 of them had numerical or structural chromosome variations while 123 had apparently normal complements. In men with apparently normal karyotypes, chromosome numbers other than 46 were found in 113 out of 2581 peripheral leucocytes analysed, or 4.2%. Hypomodal counts of less than 46 chromosomes were more frequent 3.6%, than hypermodal ones 0.6%. This is in agreement with observations made by de la Chapelle (1962), Lindsten (1963), Gustavson (1964) and others.

While non-disjunction may occur occasionally during mitosis, the majority of non-modal cells observed showed no consistency in karyotype and this was accepted as indicating variation caused by technical errors. The observations on the mitotic chromosomes of each patient have been summarized in Table A of the Appendix.

## Patients with Apparently Normal Karyotypes

A normal male chromosome complement was found in 120 men by karyotype analyses of cultured leucocytes from samples of peripheral blood (Fig. 1a). In 3 additional cases the interpretation was based on examination of cells derived from skin or testicular biopsy specimens or both. Normal karyotypes were found in supplementary analyses of cells derived from testicular biopsy material in 28 of these 123 men and in cells derived from skin cultures in 7 of them.

All cells with non-modal chromosome numbers were further analysed and their karyotypes were determined. However, it should be emphasized that mosaicism cannot be excluded when a limited number of cells derived from peripheral blood, or only one tissue have been analysed.

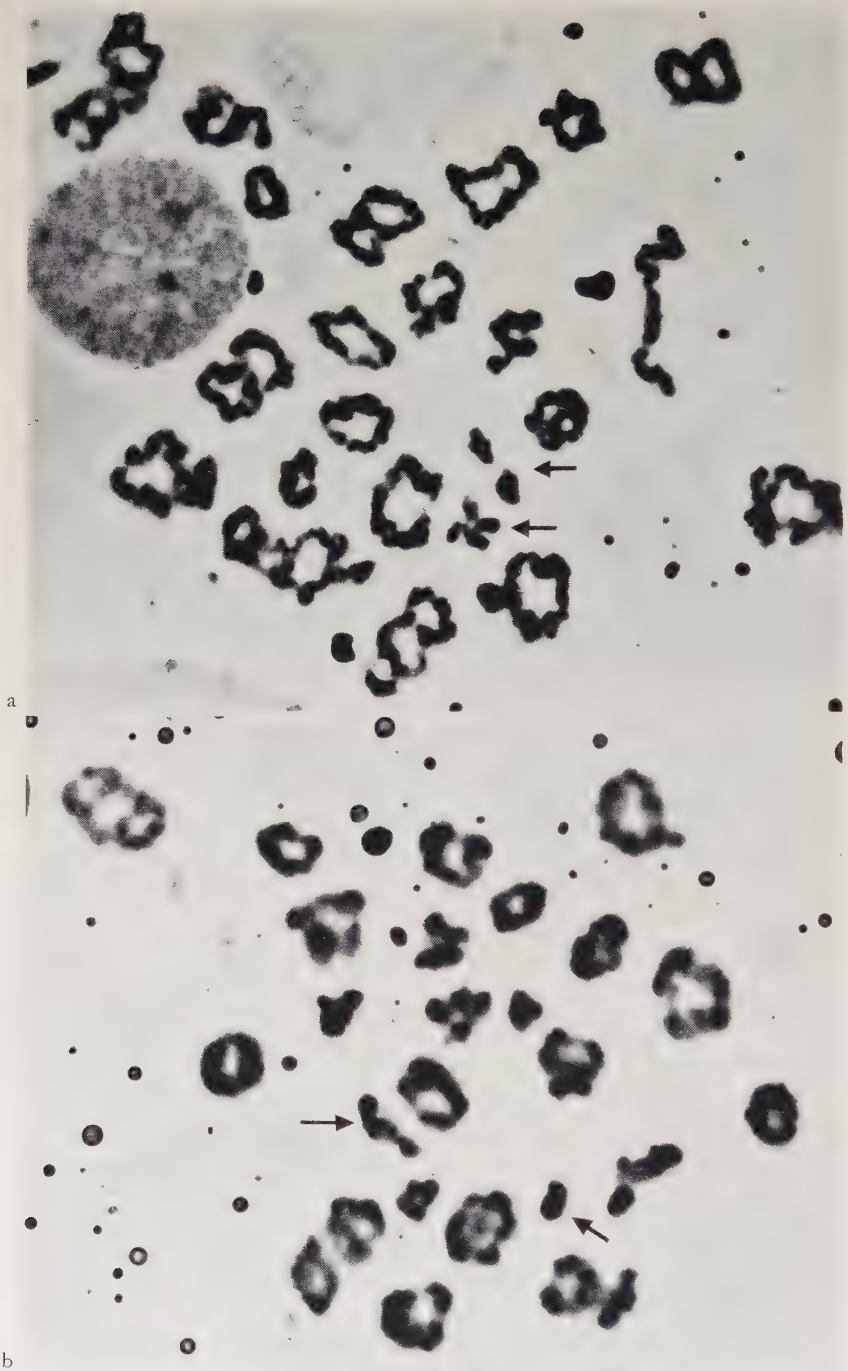



*Fig. 2.* Meiotic diakineses—metaphases I of a normal male. – *a*) Primary spermatocyte with the X and Y chromosomes associated 'end-to-end'. The arrows indicate the smallest, possibly G (21–22) chromosome bivalents. – *b*) Primary spermatocyte with the X and Y chromosomes appearing as univalents. The arrows indicate the X and Y chromosomes.

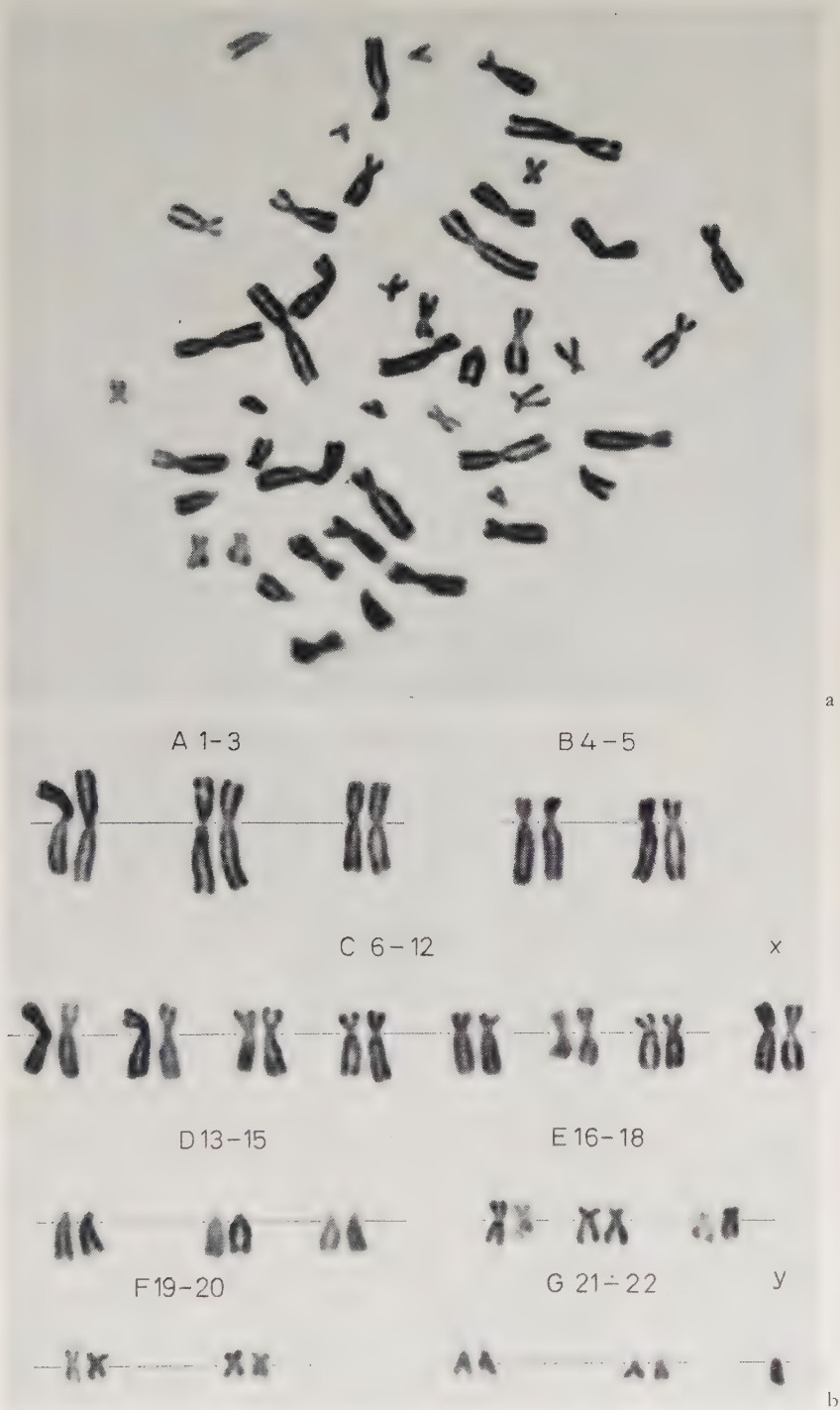



*Fig. 3.* Mitotic metaphase and corresponding karyotype of a sex chromatin positive male (case No. 120) with micro-orchidism (Klinefelter's syndrome) and 47/XXY karyotype. - Cultured leucocyte.

## Karyotypes of the 47/XXY Constitution

Two patients, case No. 120 and case No. 121, had a chromosome number of 47. The extra chromosome belonged to the C or 6-X-12 group and its size and form agreed with those of an X chromosome (Fig. 3). The finding of chromatin bodies in the interphase nuclei of cells from buccal mucosa in both patients gave further evidence in favour of a probable 47/XXY karyotype. All autosomes appeared normal.

## Karyotype with a Supernumerary Chromosome of Unknown Origin

With respect to case No. 85, the modal chromosome number was 47 in cultured leucocytes from peripheral blood as well as in cells derived from skin. The additional chromosome was approximately the size of the chromosome of the G or 21–22 group but apparently metacentric (Fig. 4). Its origin could not be established by analysis of morphological features alone nor by the autoradiographic methods of ATKINS *et al.* (1963). Buccal mucosa smears were sex chromatin negative. On the other hand, signs and symptoms presented by this patient (see Table D of Appendix) strongly indicated a sex chromosome origin. The extra chromosome could be a deleted X chromosome, too small to produce a detectable sex chromatin body, or an abnormal Y chromosome. The rest of the chromosomes, including the X and Y chromosomes, were of normal appearance. The mother had an apparently normal female karyotype by analysis of peripheral blood leucocytes. The father was deceased and one brother, also childless, could not be examined.

## Mosaics of the 46/47–XY/XXY Type

Three patients, cases No. 55, 115 and 123, had 2 cell lines with different chromosome numbers and karyotypes in cells from blood as well as other tissues.

In case 55 cultured cells derived from blood, skin and testis were examined. Sixty of the cells had 46 chromosomes and an apparently normal karyotype, whereas 121 cells had 47 chromosomes including an extra X chromosome. One sex chromatin body was found in 70% of cell nuclei in buccal mucosa smears. The proportions of the 2 cell types

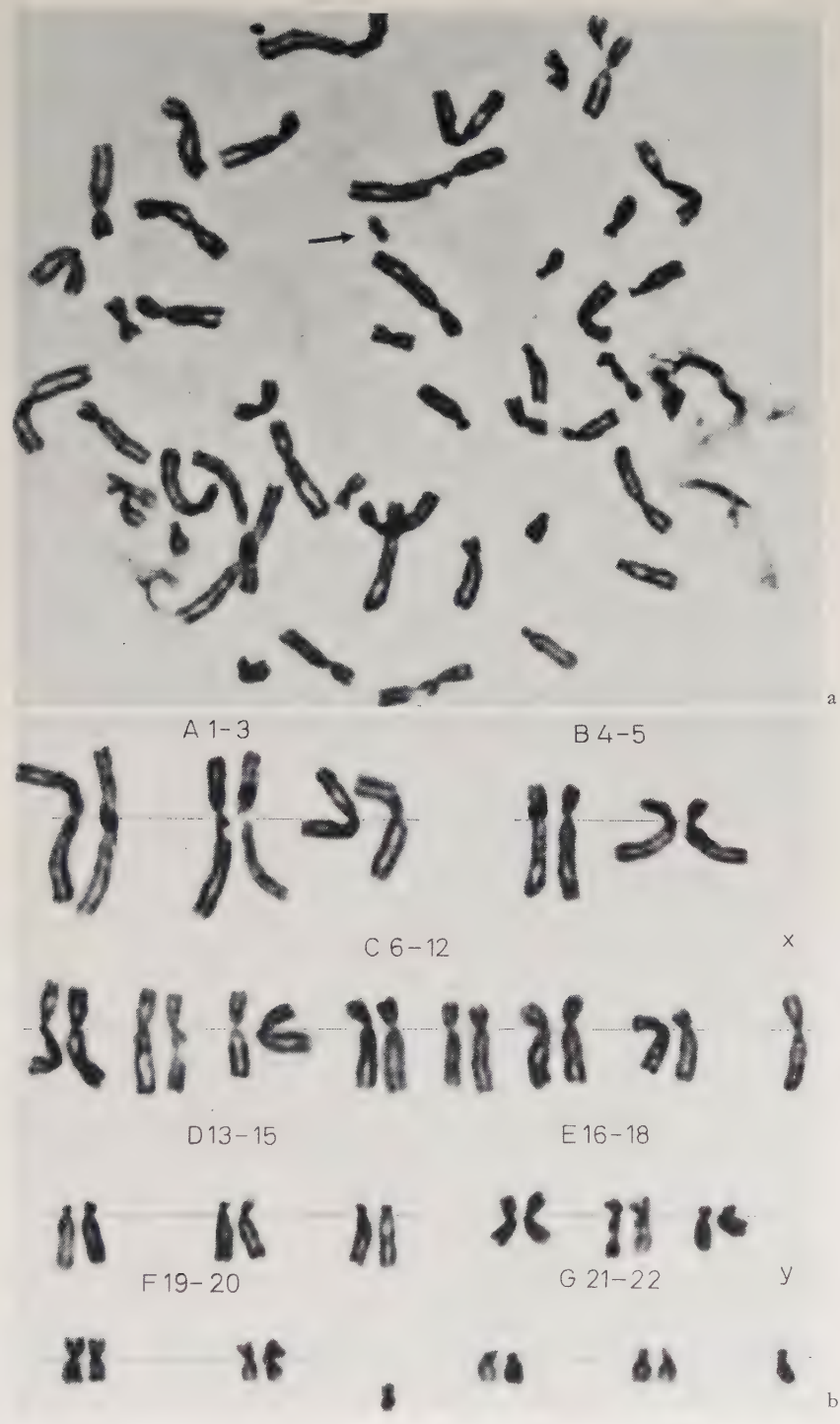



*Fig. 4.* Mitotic metaphase and corresponding karyotype of case No. 85. The arrow indicates the extra, minute chromosome. Cultured leucocyte.

varied with the type of tissue analysed (see Table A of the Appendix). The highest proportion of XXY karyotypes, *i.e.* 29/1 was found in cells derived from a skin biopsy whereas in cells derived from testicular and peripheral blood specimens, the proportions were 25/5 and 67/54.

Cells derived from skin and blood specimens were analysed in case No. 115. Both samples of cultured cells contained 2 cell lines differing in karyotype. About 90% of the cells had a normal male complement and about 10% had 47 chromosomes including an extra X chromosome. Cells with hypomodal counts showed no consistency of karyotype. The patient was interpreted as a chromosomal mosaic of the XY/XXY type. No sex chromatin bodies were found in the nuclei of the buccal mucosa smears.

Chromosomal mosaicism of the same type was revealed in case No. 123 where cells derived from one testicular and two independent blood specimens were analysed. The XY/XXY proportions were 28/74 for blood and 9/34 for testis. This patient was sex chromatin positive in buccal mucosa smears and was also interpreted as an XY/XXY mosaic.

### Mosaics of the 45/46-XO/XY Type

Two blood cultures and cultures from 1 skin biopsy specimen were examined in case No. 6. Two cell lines were present in all cultures. One line had 45 chromosomes and lacked a small acrocentric chromosome. As the remaining chromosomes of the G or 21–22 group all seemed to match well and none had the morphological features characteristic of a Y chromosome, the karyotype of these cells was interpreted as 45/XO. All other cultured displayed a normal male karyotype. Thus the patient was regarded as a chromosomal mosaic of the XO/XY type.

In case No. 80, the examination of 2 independent cultures of peripheral blood taken at different times disclosed the same type of mosaicism with XO/XY proportions of about 20/104. The patient refused biopsies of skin or testis. However there should be no reasonable doubt that this patient was a chromosomal mosaic of the XO/XY type.

### A Complex Mosaic, Presumably of 45/46/47-XO/XY/XxO/XxY Type

Analysis of a total of 242 cells in case No. 79 derived from 2 independent cultures of peripheral blood taken at different times as well as from

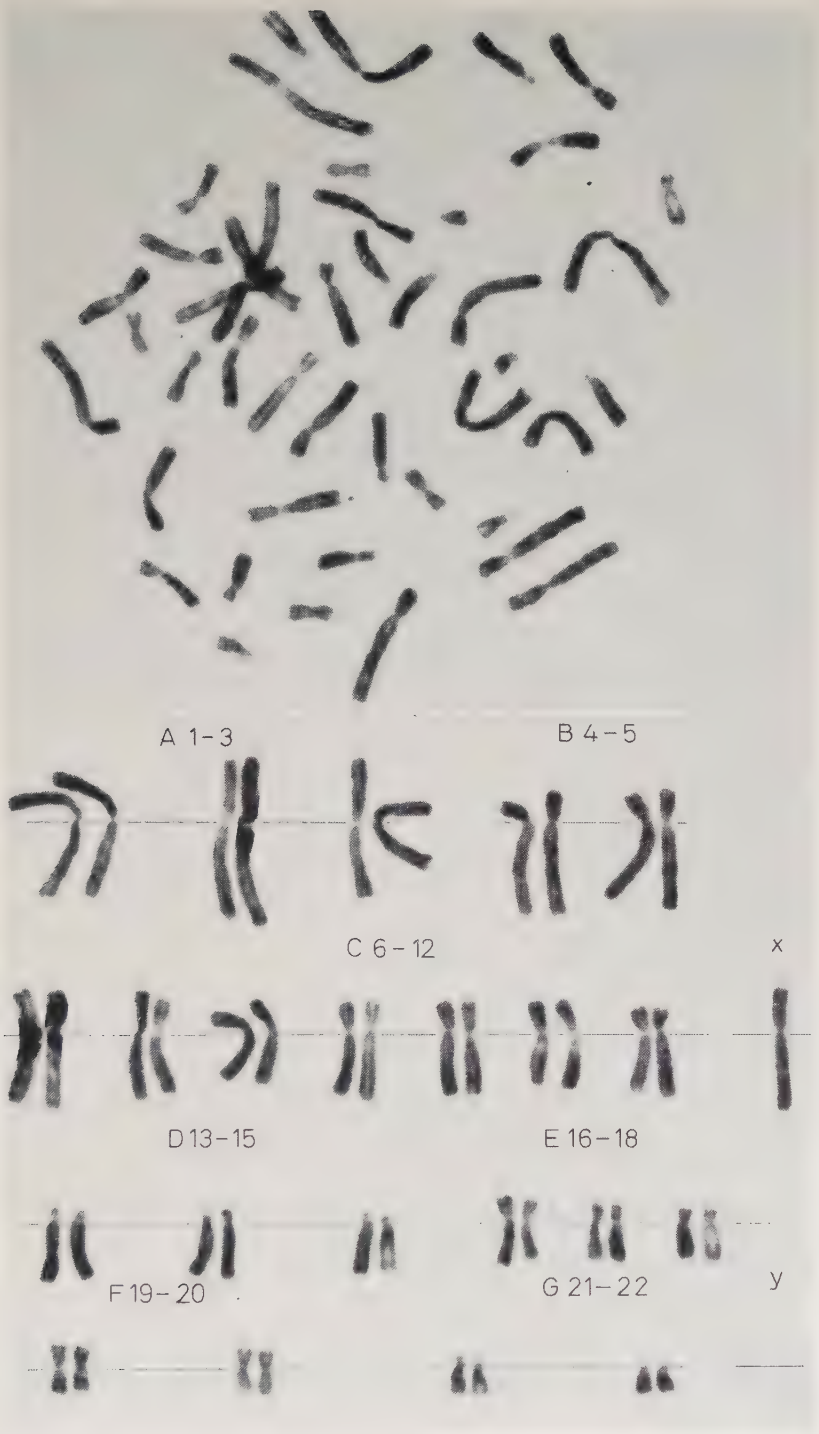



*Fig. 5.* Mitotic metaphase and corresponding karyotype of case No. 79. – Cultured leucocyte. The Y chromosome is missing.

*Fig. 6.* a) Mitotic metaphase and – b) corresponding karyotype of case No. 79. Cultured leucocyte. Normal karyotype.

*Fig. 7.* a) Mitotic metaphase and – b) corresponding karyotype of case No. 79. Cultured leucocyte. The Y chromosome is missing and an extra, metacentric chromosome is present, and placed between the F19 20 and Q21–22 groups in the karyotype.

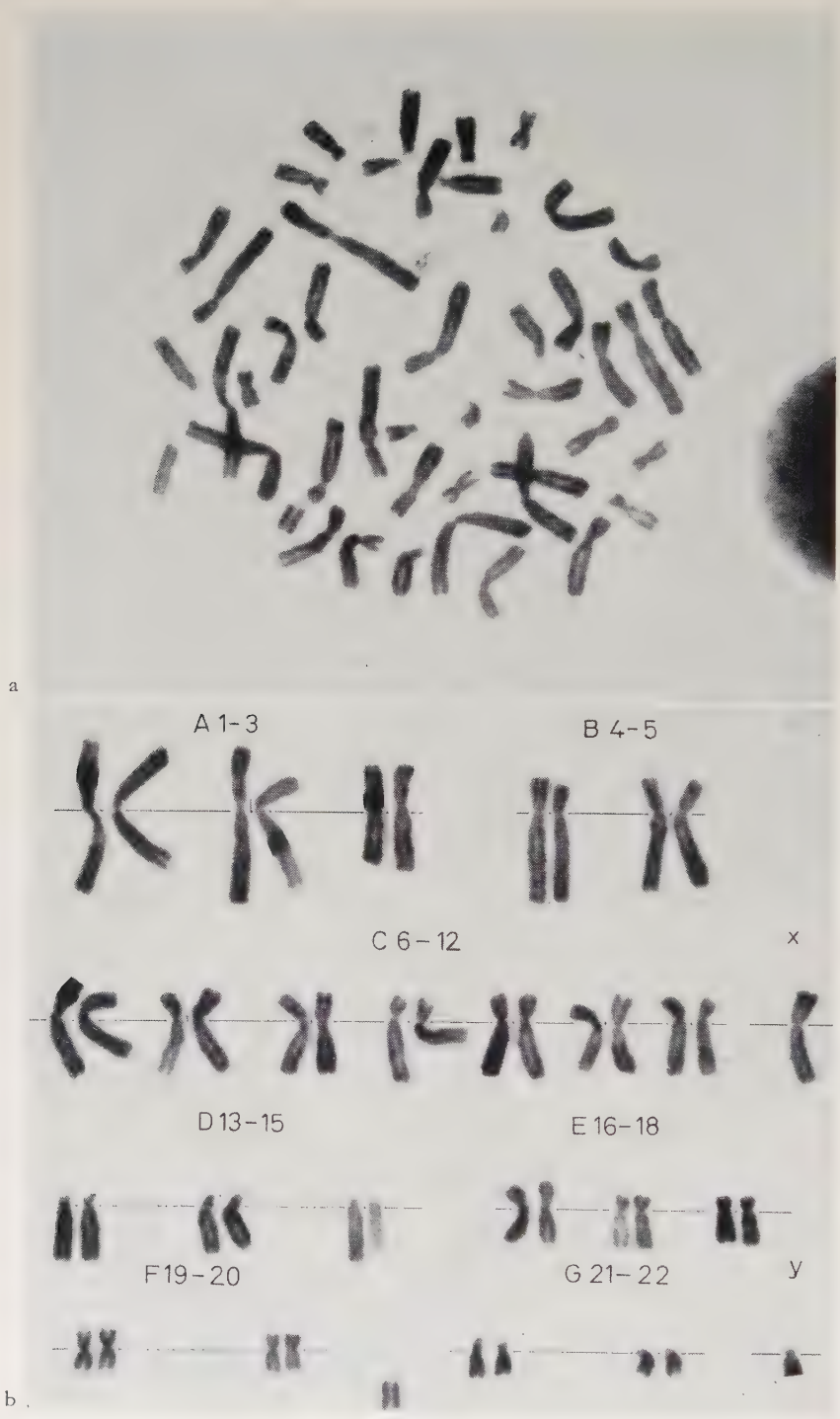
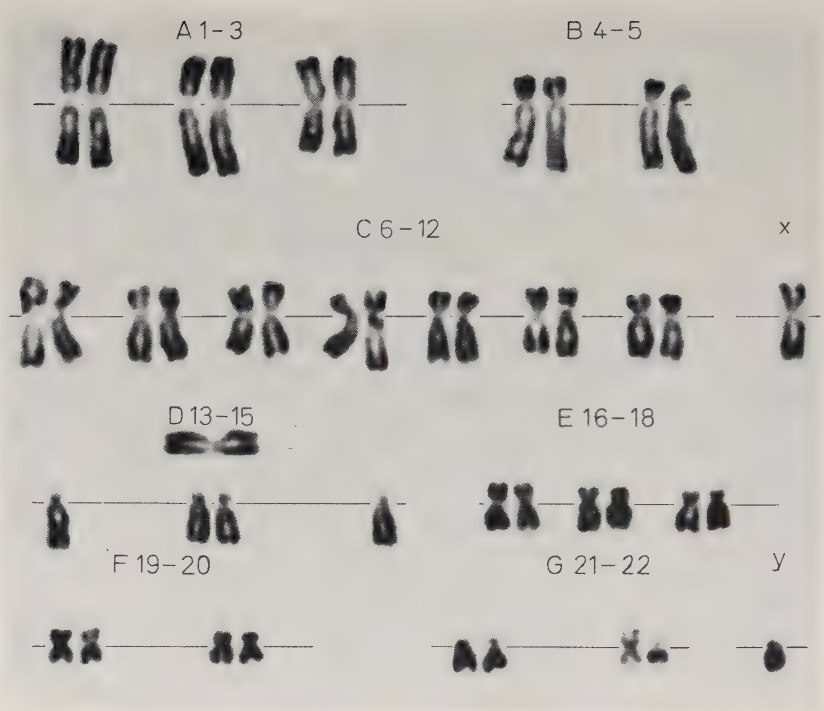



*Fig. 8.* a) Mitotic metaphase and – b) corresponding karyotype of case No. 79. Cultured leucocyte. In addition to a normal male chromosome complement an extra metacentric chromosome is present and placed between the F 19–20 and G 21–22 groups in the karyotype.

2 separate cultures of testicular tissue and 1 skin culture, indicated the presence of 4 cell populations with different karyotypes (Fig. 5–8). Two different karyotypes were found in cells derived from 2 testicular and 1 skin biopsy specimens. The chromosome number of these aberrant cells was 45. All such cells examined had only 4 small acrocentric chromosomes. As these could be matched into two pairs the missing chromosome is likely to be the Y. All other cells examined had a normal male chromosome complement except for a few with hypomodal numbers and inconsistent karyotypes. By contrast, cultured blood leucocytes were shown to belong to 4 different cell populations with distinct karyotypes. Two of these populations were identical with those found in the material from testis and skin, *i.e.* their karyotypes were interpreted as 45/XO and 46/XY. The third population had 46 chromosomes in cells which apparently lacked the Y chromosome but in addition had a new small chromosome. This new chromosome had the size of an F group chromosome but a centromere location which matched none of the normal autosomes. This aberrant chromosome was observed in 4 out of 81 cells with 46 chromosomes and also in a fourth celltype, *i.e.* in 5 out of 6 cells with 47 chromosomes where it occurred in addition to a normal male complement. The origin of the aberrant chromosome could not be established by analysis of morphological features, and no sex chromatin bodies were found in interphase nuclei from buccal mucosa smears. As examination of the patient revealed no signs of physical defects or abnormalities of development the deviating chromosome was tentatively classified as a deleted X. It may however also be a structurally rearranged Y chromosome of the pericentric inversion type. The allegedly deleted X was found in some cultured leucocytes only, and even if it should occur in other cell types the proportions of such XxY or XxO cells would probably not be high enough to produce a chromatin positive buccal mucosal smear. With these reservations, the patient was classified cytogenetically as an XO/XY/XxO/XxY mosaic.

## Autosomal Translocation Heterozygosity

Case No. 110 had 45 chromosomes in cultured leucocytes as well as in cultured cells derived from skin and testicular biopsy specimens. All cells had an apparently normal XY pair, 4 chromosomes only in the D or 13–15–group and 3 large metacentric chromosomes of the No. 3 category (Fig. 9a). One of the chromosomes closely resembling a No. 3

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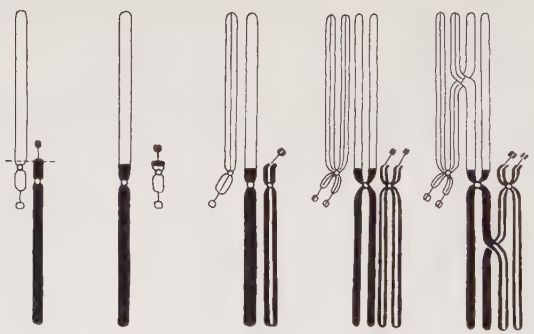

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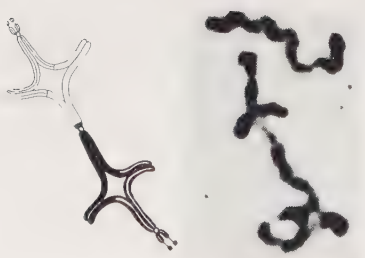

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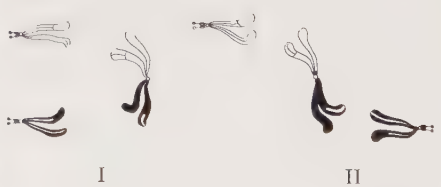


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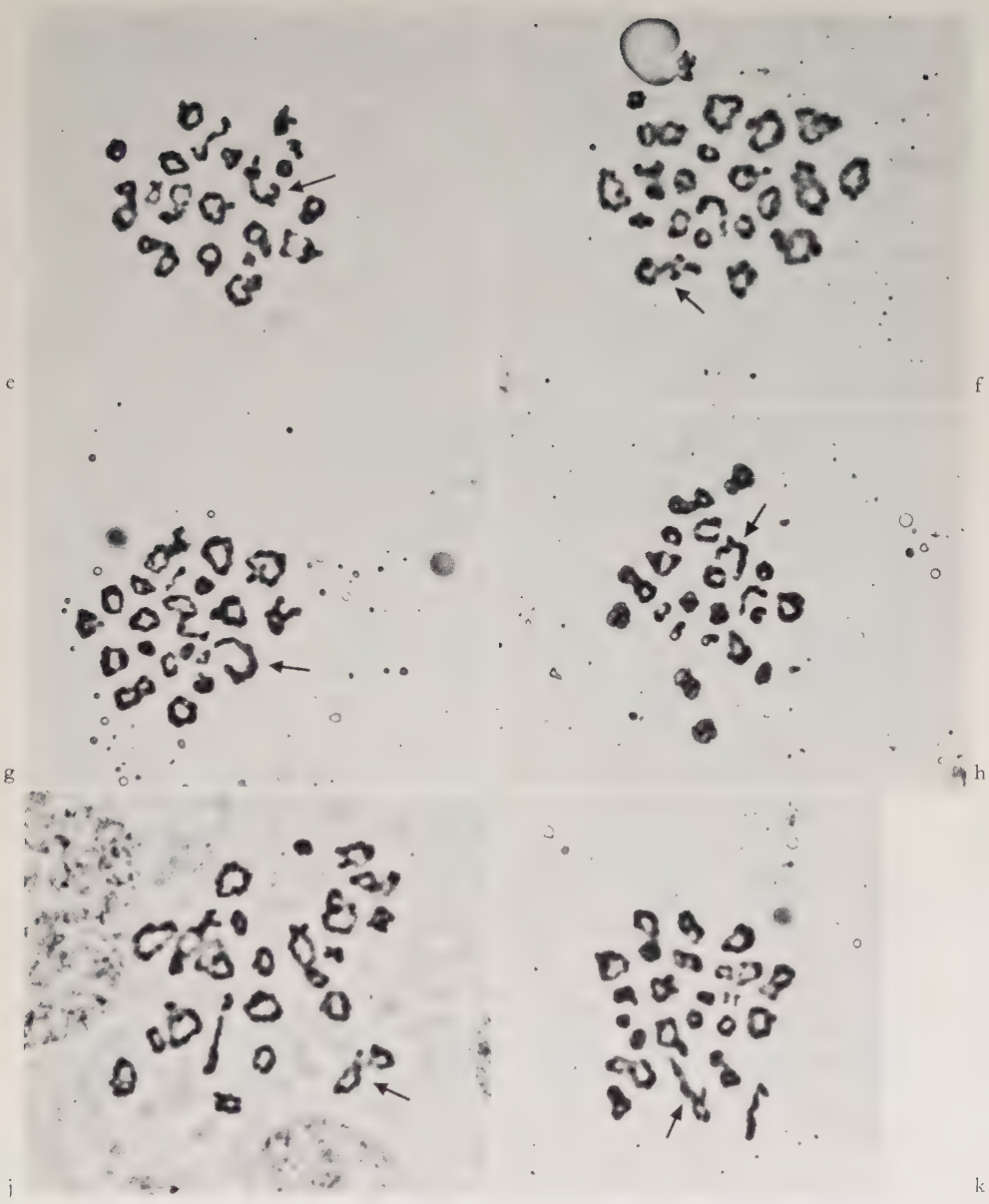



*Fig. 9. a*) Karyotype of a balanced carrier of a D/D translocation chromosome. The alleged translocation chromosome is placed above the remaining D-group chromosomes. – Cultured fibroblast from testis. – *b*) Possible origin and expected pairing of the D/D translocation chromosome and its homologues during first meiotic prophase. – *c*) Expected appearance of the $D_1$–$D_1/D_2$–$D_2$ trivalent during diakinesis and metaphase I (to the left) and real appearance (to the right). The sex bivalent is seen on top. – *d*) The chromosomes involved in the trivalent are likely to be distributed on the daughter cells in two main classes giving rise to different types of balanced gametes (I) and unbalanced gametes (II). *e -k*) Meiotic diakineses and metaphases I. 21 bivalents, including the XY bivalent, together with the abnormal trivalent which is indicated by arrows. Two chiasmata are seen in Figs. *j* and *k* which are situated on one and the same side of the centromeric region of the translocation chromosome.

was interpreted as consisting of the major parts of the 2 missing D, or 13–15 chromosomes, joined through a translocation process or a centric fusion. Critical information on origin and constituent parts of structurally changed chromosomes is rarely obtained by analysis of mitotic chromosomes only, but requires observations on their behaviour during meiosis. In this case none of the examined cells in mitotic metaphase had any chromosomal body present which could be suspected for a minute translocation chromosome or even a fragment. Should such a chromosome originally have been formed it is likely to have disappeared during subsequent divisions. Observations on the meiotic divisions in preparations from a testicular biopsy specimen gave sufficient critical information for a clear identification of the patients karyotype. A large trivalent association, easily identified as containing one large metacentric and two large acrocentric chromosomes was observed at diakinesis and metaphase I (Fig. 9). In addition the observation of true chiasma formations between the paired chromatids of this trivalent proves, that the new large metacentric chromosome actually consists of 2 joined heterologous D-chromosomes. These could, however, not be further identified, due to lack of identity criteria. A short note on the findings in this patient was published earlier by KJESSLER (1964). The patient's mother and one brother had normal karyotypes. The father and another brother had both died of tuberculosis.

## Variations of the Y Chromosome

An extremely small chromosome, assumed to be a deleted Y chromosome, was observed in all examined cells derived from case No. 108 (Fig. 10). Cultured cells were obtained from biopsy specimens from both testes and from peripheral blood. The autosomes and the X chromosome were apparently normal. The patient was an only child and his father was dead. His paternal uncle, who had a history of involuntary childlessness without known cause, was also shown to carry the same distinctive Y chromosome in cultured blood leucocytes.

In another patient, case No. 119, the Y chromosome was much larger than usual. It was very much like one of the large acrocentric chromosomes of the D or 13–15 group and it was not always possible to decide which was the Y (Fig. 11). The observations were made on cultured blood leucocytes only and the X chromosome together with the autosomes were apparently normal. The father of this patient and his one and only sibling, a brother, were not available for examination.

*Fig. 10.* Mitotic metaphase and corresponding karyotype of a patient (case No. 108) with a small, possibly deleted Y chromosome. Cultured skin fibroblast.

*Fig. 11.* Mitotic metaphase and corresponding karyotype of a patient (case No. 119) with a large Y chromosome. Cultured leucocyte.

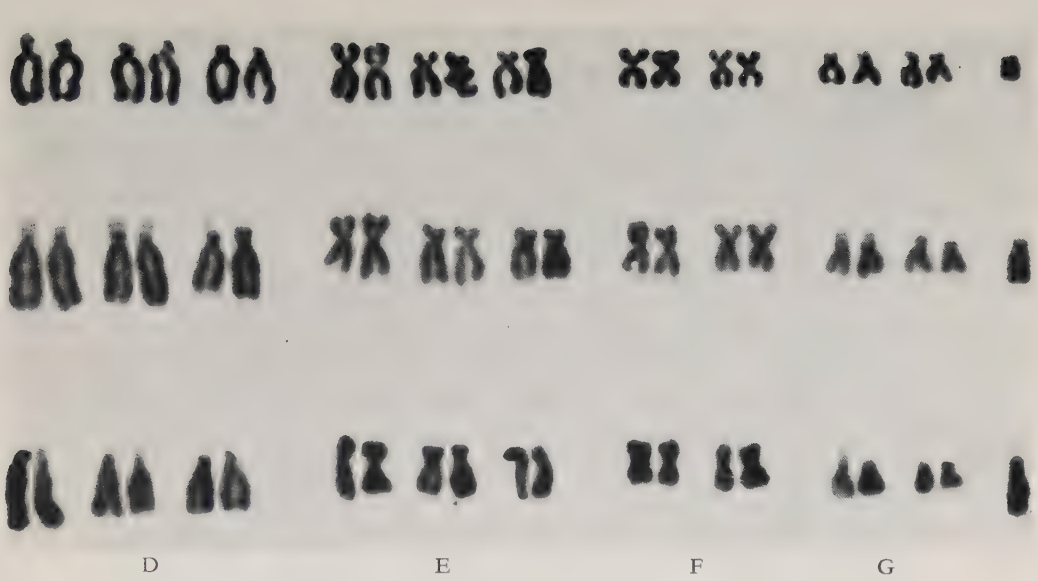



*Fig. 12.* Comparison between relative lengths of the Y chromosomes and the D, E, F and G group chromosomes in 1 patient with a possibly deleted Y chromosome (case No. 108; top row), 1 normal male (mid row) and 1 patient with a large Y chromosome (case No. 119 bottom row).

### *Meiosis*

The important observations for each examined individual have been summarized in Tables B 1 and B 2 of the Appendix.

### Sex Chromosomes

The interrelationship between the X and Y chromosomes during diakinesis and metaphase I was studied in 692 primary spermatocytes from 30 patients. In 95,6% of such cells from men with apparently normal karyotypes the X and Y chromosomes showed an 'end-to-end' association (Fig. 2a). In 4.4% of the cells there was no association at all, *i.e.* the X and Y chromosomes appeared as univalents (Fig. 2b).

Two patients, case No. 6 and case No. 79, had some cells with one X chromosome only, as observed at diakinesis and metaphase I (Fig. 13). However the cultured blood leucocytes of both patients were mainly a mixture of XO and XY cells. Because the Y chromosome was regularly identified at diakinesis and metaphase I in patients with normal karyotypes, the observation of XO primary spermatocytes in these two XO/XY and XO/XY/XxO/XxY mosaics only is unlikely to be an

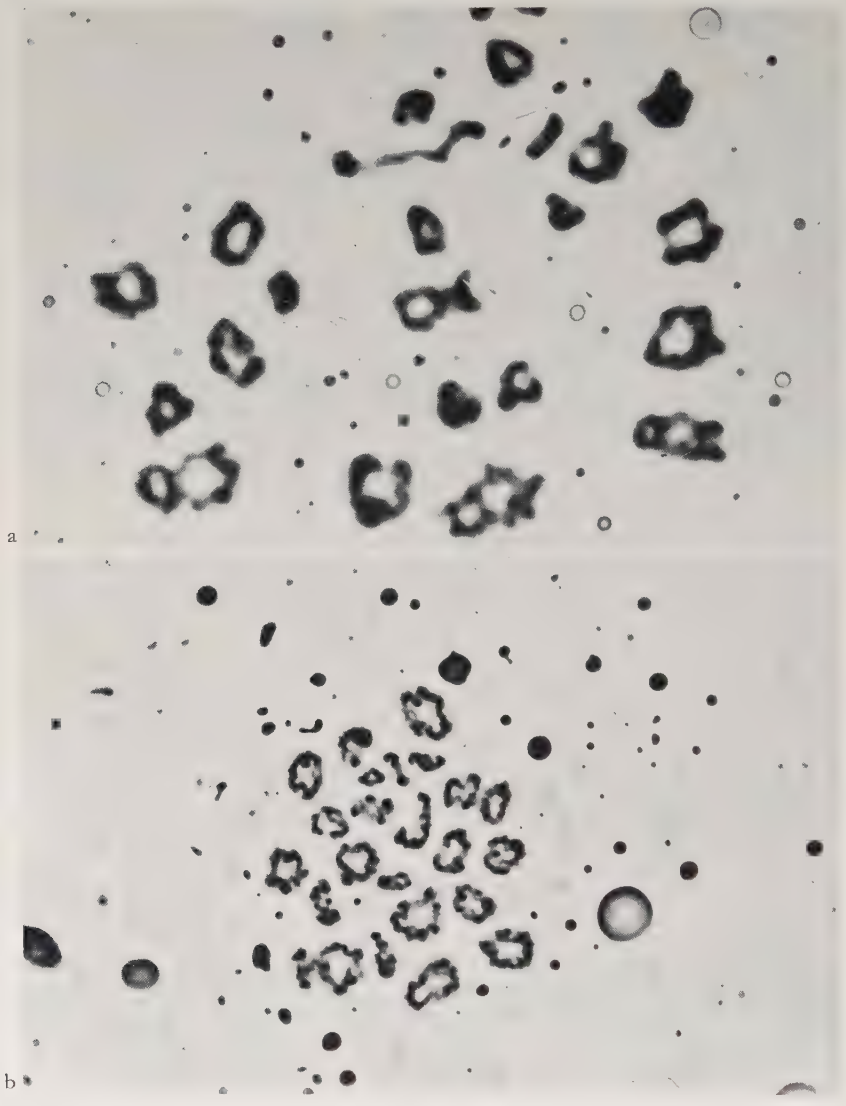
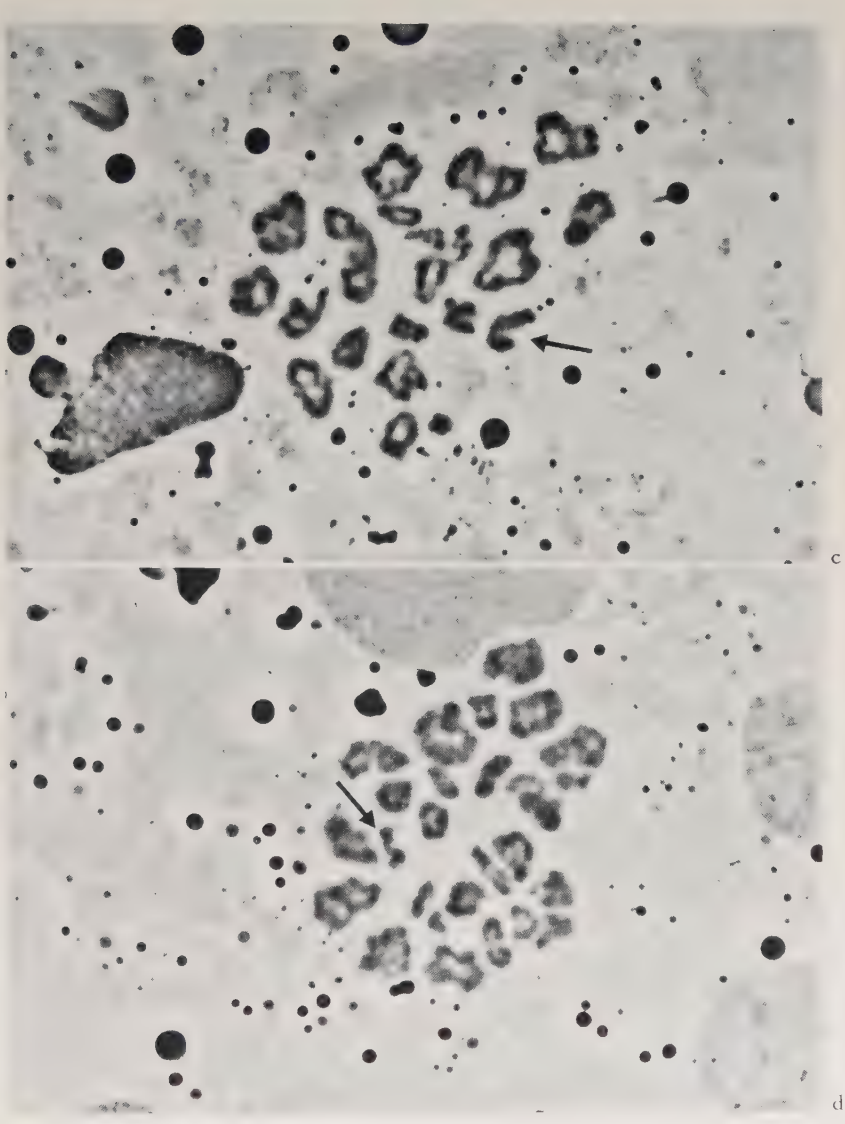



*Fig. 13.* Meiotic diakineses and metaphases I of 2 patients (case No. 6 and case No. 79). *a*) Primary spermatocyte at diakinesis with clear XY bivalent (Case 6). – *b*) Primary spermatocyte at diakinesis with questionable XY bivalent (Case 79). – *c-f*) Primary spermatocytes at diakinesis and metaphase I with a single X sex chromosome (indicated by arrows). (*c* and *d*): Case 6, *e* and *f*): Case No. 79).

artefact. It is therefore concluded that in some cases of XO/XY and XO/XY/XxO/XxY mosaicism the germinal cell population may consist of primary spermatocytes with a XO sex chromosome constitution



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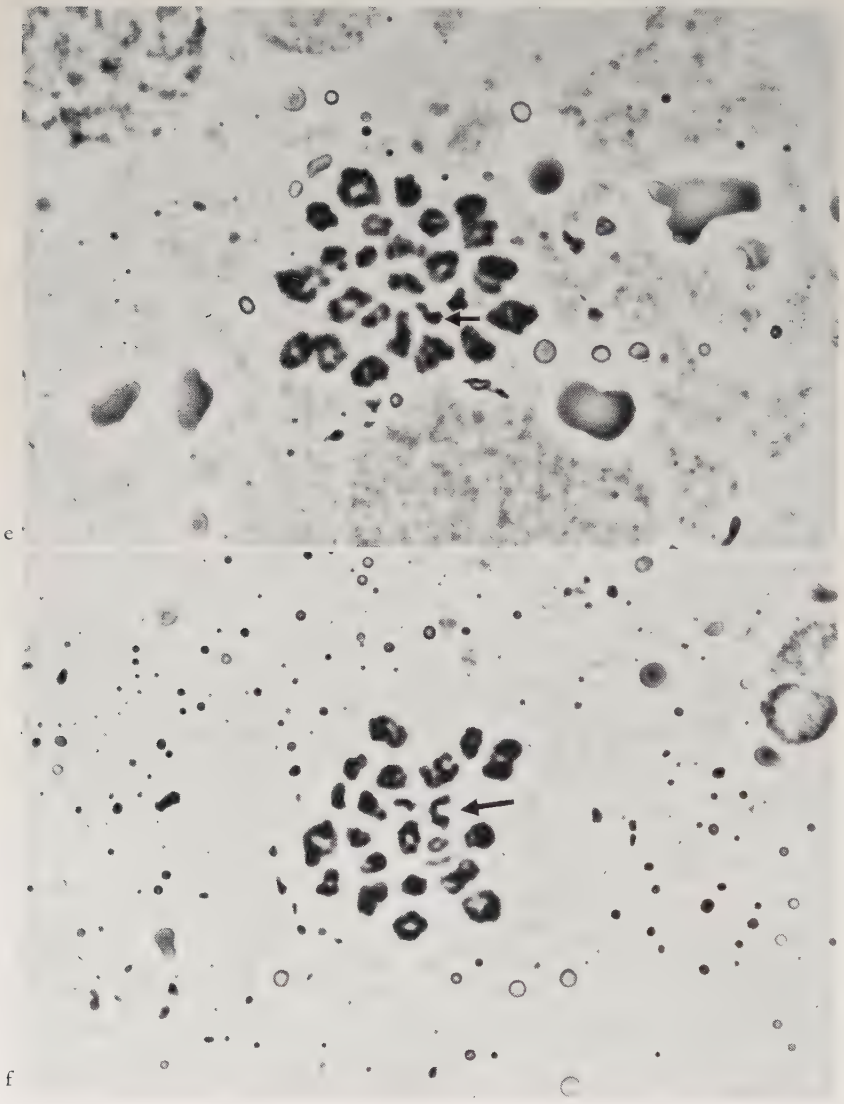
in addition to chromosomally normal cells. A third case of XO/XY mosaicism was not available for meiotic studies.

In this material, the proportion of spermatocytes with an end-to-end association of the sex chromosomes to those having the X and Y as univalents was not significantly different when spermatocytes derived from individuals with normal karyotypes were compared with spermatocytes derived from individuals with aberrant karyotypes.




## Autosomes

A total of 15,230 autosome configurations of 692 primary spermatocytes at diakinesis and metaphase I which were derived from 30 patients has been analysed. In all patients, except case No. 110, the autosomes always appeared as typical bivalent structures. Their chromatid arms were joined by one or more chiasmata. Autosomal univalents were not

observed at the examined stages of meiosis. These observations indicate a high degree of precision and regularity of pairing and chiasma formation in the autosomal complement.

In case No. 110 all examined diakineses and metaphases I contained a chromosome configuration larger than the XY bivalent and therefore easy to identify. The remaining autosomes were represented as 20 configurations, all apparently normal bivalents. The interpretation of this large and unusual chromosome structure as a trivalent became clear on close inspection and revealed further indirect support from the number and appearance of the mitotic chromosomes of this patient (Fig. 9.)

Most likely, this trivalent consisted of all but a minute non-vital part of two heterologous D chromosomes joined by translocation or centric fusion and, in addition, the 2 $D_s$-chromosomes homologous with the two respective arms of the translocation chromosome. This would leave the 2 remaining chromosomes belonging to the D(13–15) group free to form their regular bivalent (Figs. 9e–k). All cells totalled 22 chromosome bodies only.

The total number of chiasmata per cell, as well as the number of terminal chiasmata per cell, were determined in 692 primary spermatocytes at stages from diakinesis to metaphase I. The spermatocytes were derived from 30 patients belonging to the present series. The average number of chiasmata per cell and a mean terminalization coefficient were determined for each individual. The detailed results are given in Table B 2 of the Appendix. From these figures, it follows that there is apparently no significant difference in the average terminalisation coefficient between the individuals belonging to this sample regardless

*Table I. Mean chiasma frequencies per cell and mitotic karyotypes of 30 men attending an infertility clinic*

| Karyotype interpretation | No. of pat. | Case No. | No. of cells analysed | Number of chiasmata per cell range | average | Terminalisation coefficient mean |
|---|---|---|---|---|---|---|
| 46 / XY normal | 25 | – | 550 | 43–64 | 52.7 | 0.64 |
| 45 / 46 XO / XY | 1 | 6 | 22 | 44–55 | 50.9 | 0.64 |
| 45 / 46 / 47 XO / XY / XxO / XxY | 1 | 79 | 30 | 44–59 | 52.9 | 0.60 |
| 46 / Xy | 1 | 108 | 30 | 46–57 | 51.0 | 0.68 |
| 46 / 47 XY / XXY | 1 | 115 | 30 | 49–59 | 53.3 | 0.65 |
| 45 / XY T: D/D | 1 | 110 | 30 | 39–54 | 47.0 | 0.63 |

of karyotype. A direct comparison may thus be made between the individuals with regard to average chiasma frequencies per cell. Furthermore, the distribution of chiasmata per bivalent was determined in each cell and an average value was calculated for each individual. The detailed results are presented in Table B 2 of the Appendix.

The average number of chiasmata per cell in 550 primary spermatocytes derived from 25 men with apparently normal karyotypes and attending an infertility clinic, was found to be 52.7 ranging from 43 to 64 (Table I).

This value is somewhat lower than that found by FORD and HAMERTON (1956) who determined the mean chiasma frequency in a cell population of 23 cells derived from 3 men and found it to be 55.9 with a range of 50 to 63.

In Table I mean chiasma frequencies per cell are given for individuals with different karyotypes (Table I).

The patient with the D/D translocation was found to have a significantly lower number of chiasmata per cell in comparison with patients with normal karyotypes, as well as those with sex chromosome anomalies. By contrast, no apparent difference could be demonstrated in the mean chiasma frequencies of patients with normal karyotypes and patients with sex chromosome anomalies. (see Table B 2 of the Appendix). The D/D translocation chromosome present in the complement thus seems to exert an interchromosomal influence by impairing chiasma formation between the other homologous autosomes.

The chiasma frequencies in cells with associated sex chromosomes, free sex chromosomes and cells without a Y chromosome have been compared. To represent cells with the sex chromosomes associated end-to-end, only those seen immediately before or after the other types of cells mentioned were chosen.

The results are shown in Table II. No difference in the mean numbers of chiasmata per cell could be demonstrated in the 3 types of cell described. Thus no direct correlation could be shown between sex chromosome association and autosome associations in cells at diakinesis and metaphase I. Absence of a Y chromosome in the complement did not seem to interfere with chiasma formation among the autosomes either.

An analysis of the distribution of chiasmata per autosomal bivalent in the 25 men with apparently normal karyotypes belonging to the present series showed that 16.2% of the bivalents had 1 chiasma only. This implies that on the average each primary spermatocyte at diakinesis

or metaphase I has 3.6 bivalents with one chiasma only. The majority of bivalents had 2 or 3 chiasmata, *i.e.*, 39.7 and 33.4% respectively, while 9.6 and 1% had 4 and 5 chiasmata each. Very few bivalents with 6 chiasmata were found (Table III).

As shown in Table B 2 of the Appendix, no cell had less than 2 single-chiasma-bivalents. These 2 bivalents were consistently found to be the smallest ones and appeared cross or rod shaped (Fig. 2a). Apparently these 2 small bivalents consist of the 2 homologous pairs of chromosomes belonging to the G or 21–22 group. The shape of these bivalents shows that in each of them the chiasma is located in the long arm. In the majority of cells these bivalents had a simple, symmetrical cross-shaped appearance suggesting that the chiasma observed in each bivalent might be the only one formed. As an average number of 3,6 autosomal bivalents containing a single chiasma were observed in each cell at diakinesis and metaphase I, at least one more pair of homologous chromosomes, other than the members of the G or 21–22 group, should be joined by a single chiasma only. The observed larger bivalents with single chiasmata could usually be interpreted as consisting of a pair of chromosomes belonging to the D or 13–15 group. The symmetrical cross-shape of this larger bivalent, or sometimes its appearance as a long rod, implied that the only chiasma formed between the homologous partners in this bivalent association, was situated in the long arm region. This is consistent with the findings in the small acrocentric chromosomes. The morphology of the D or 13–15 group chromosomes, which are known to have small short arms, also lends support to such an interpretation. Chiasmata were otherwise usually observed in both chromosome arms, even in chromosomes which are known to be smaller than the members of the D or 13–15 group.

Patients with normal karyotypes and those with sex chromosome anomalies were also analysed with regard to the distribution of chias-

*Table II. Mean chiasma frequencies per cell in cells with associated respectively free sex chromosomes and in cells without a Y chromosome*

| Sex chromosome association and constitution of the cells analysed | No. of pat. | No. of cells analysed | No. of chiasmata per cell range | mean | Terminalisation coefficient mean |
|---|---|---|---|---|---|
| X and Y associated 'end-to-end' | 18 | 64 | 43–60 | 51.8 | 0.64 |
| X and Y free | 18 | 32 | 46–59 | 52.5 | 0.65 |
| Y lacking (XO) | 2 | 13 | 48–58 | 53.2 | 0.61 |

*Table III. Distribution of chiasmata per bivalent and mitotic karyotypes in 29 men attending an infertility clinic*

| Karyotype interpretation | No. of pat. | Case No. | No. of bivalents analysed | Nos. and percentages of bivalents with the following numbers of chiasmata per bivalent: 1 | | 2 | | 3 | | 4 | | 5 | | 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| 46 / XY normal | 25 | – | 12,100 | 1963 | 16.2 | 4808 | 39.7 | 4040 | 33.4 | 1165 | 9.6 | 119 | 1.0 | 5 | 0.01 |
| 45 / 46 XO / XY | 1 | 6 | 484 | 79 | 16.3 | 217 | 44.8 | 151 | 31.2 | 37 | 7.6 | 0 | 0 | 0 | 0 |
| 45 / 46 / 47 XO / XY / XxO / XxY | 1 | 79 | 660 | 106 | 16.1 | 259 | 39.2 | 219 | 33.2 | 73 | 11.1 | 3 | 0.5 | 0 | 0 |
| 46 / Xy | 1 | 108 | 660 | 115 | 17.4 | 289 | 43.8 | 189 | 28.6 | 64 | 9.7 | 3 | 0.5 | 0 | 0 |
| 46 / 47 XY / XXY | 1 | 115 | 660 | 110 | 16.7 | 259 | 39.2 | 206 | 31.2 | 73 | 11.1 | 12 | 1.8 | 0 | 0 |

*Table IV. Distribution of chiasmata per bivalent in cells with associated respectively free sex chromosomes and in cells without a Y chromosome*

| Sex chromosome association and constitution of the cells analysed | No. of pat. | No. of bivalents analysed | Nos. and percentages of bivalents with the following numbers of chiasmata per bivalent: 1 | | 2 | | 3 | | 4 | | 5 | | 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| X and Y associated 'end-to-end' | 18 | 1452 | 251 | 17.3 | 595 | 41.0 | 466 | 32.1 | 130 | 9.0 | 10 | 0.7 | 0 | 0 |
| X and Y free | 18 | 726 | 119 | 16.4 | 292 | 40.2 | 244 | 33.6 | 67 | 9.2 | 4 | 0.6 | 0 | 0 |
| Y lacking (XO) | 2 | 264 | 37 | 14.0 | 109 | 41.3 | 85 | 32.2 | 32 | 12.1 | 1 | 0.4 | 0 | 0 |

mata per autosomal bivalent. No heterogeneity was disclosed (Table III and Table B 2 of the Appendix).

A similar analysis was made with respect to cells with associated and with free sex chromosomes and cells without the Y chromosome. As shown in Table IV the calculations do not appreciably indicate any associations between these 3 variables and the distribution of chiasmata per bivalent.

In case No. 110 the 2 heterologous D chromosomes pairing with the D/D translocation chromosomes usually had their long arms joined with the arms of the new metacentric translocation chromosome, each by a single chiasma. Occasionally, however, 2 chiasmata were observed to join the long arms of these chromosomes on one and the same side of the centromeric region of the translocation chromosome (Fig. 9j, k). No general conclusions may however be drawn from the findings in this patient regarding chiasma formation between homologous D chromosomes in general, as the structural rearrangement might have influenced the chiasma formation locally as well as generally.

### *Sperm Analysis*

A total of 1520 specimens of ejaculated seminal fluid derived from 135 men were examined with regard to sperm count and sperm morphology. Individual data about these factors have been summarized in Table A of the Appendix. From 16 patients, only 3 samples of seminal fluid could be obtained and from 2 patients only 2 samples, whereas 4 specimens were analysed from each of the remaining 117 patients.

### Sperm Count

Sperm counts were made in seminal samples derived from all 135 men. The patients were classified according to their average sperm counts in serial analyses. The distribution of the patients with regard to average sperm count and mitotic karyotype is shown in Fig. 14.

Normal karyotypes were found in patients belonging to all sperm count classes, whereas all but one of the patients with aberrant or not entirely normal karyotypes were found to belong to classes with less than 41 million sperms per ml. Two chromatin positive patients with Klinefelter's syndrome and with XXY sex chromosome constitutions were aspermic and belonged to the most severely affected patients.

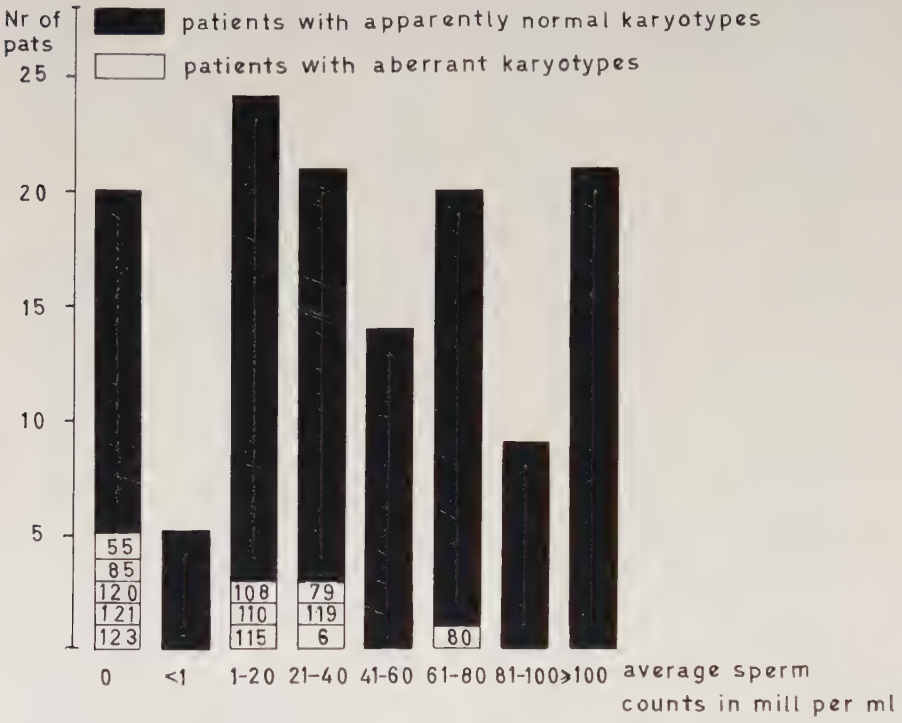



*Fig. 14.* Distribution of average sperm counts and mitotic karyotypes in 135 men attending an infertility clinic.

| | | |
|---|---|---|
| 6 | 45/46 | XO/XY |
| 55 | 46/47 | XY/XXY |
| 79 | 45/46/47 | XO/XY/XxO/XxY |
| 80 | 45/46 | XO/XY |
| 85 | 47 | XY + extra, minute chromosome of possibly sex chromosomal origin |
| 108 | 46 | X + possibly deleted y |
| 110 | 45 | XY with a D/D translocation |
| 115 | 46/47 | XY/XXY |
| 119 | 46 | X + large Y |
| 120 | 47 | XXY |
| 121 | 47 | XXY |
| 123 | 46/47 | XY/XXY |

Aspermia was also found in 2 out of the 3 patients with XY/XXY mosaicism and in 1 patient with a supernumerary chromosome of possibly sex chromosomal origin. The third of the XY/XXY mosaics was found to produce a reduced number of sperms. Two patients with Y chromosomes of unusual size both produced a reduced number of

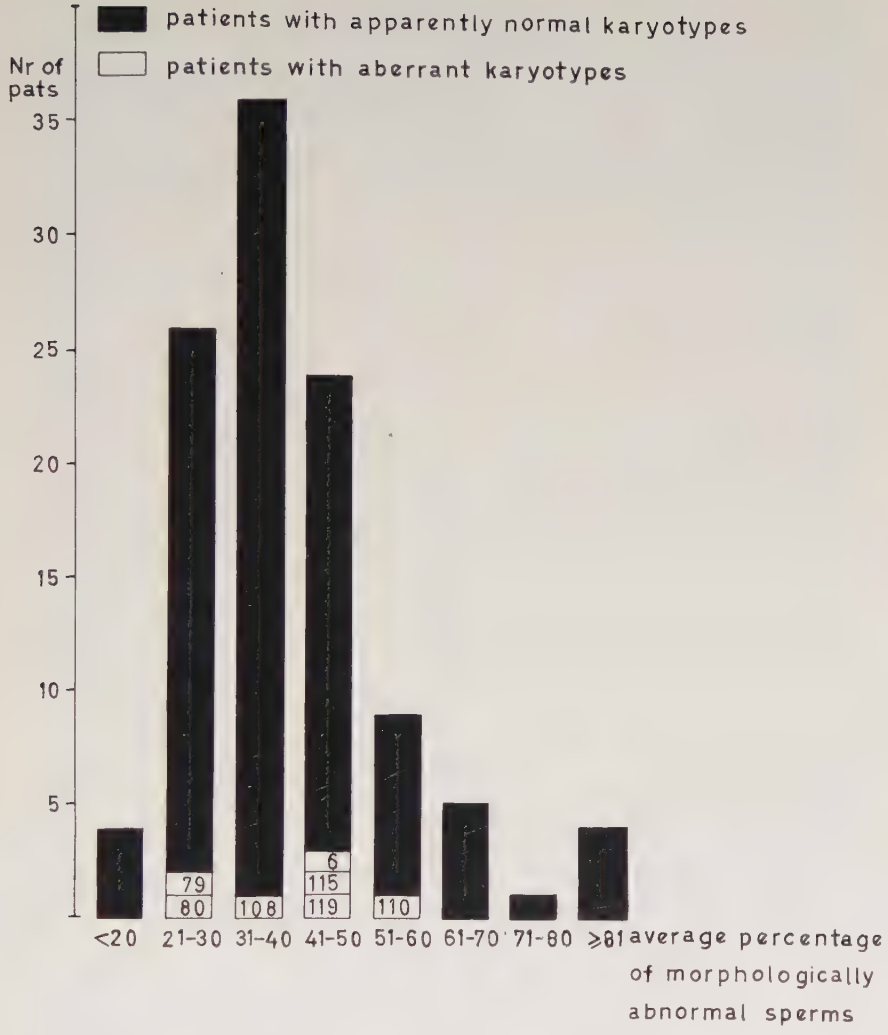



*Fig. 15.* Distribution of average percentages of morphologically abnormal sperms and mitotic karyotypes in 109 men attending an infertility clinic.
The numbers in the columns refer to the cases listed in Fig. 14.

sperms as did the carrier of the balanced D/D translocation. All 3 patients with mosaicism of the XO/XY and XO/XY/XxO/XxY types were found to be less severely affected than other patients with abnormal karyotypes. No individuals with an aberrant karyotype were found among patients with more than 81 million sperms per ml.

## Sperm Morphology

Sperm morphology was examined in seminal samples derived from 109 individuals. The patients were grouped in classes according to their average percentages of morphologically abnormal sperms. The distribution of the patients with regard to sperm morphology and mitotic karyotype is demonstrated in Fig. 15.

Patients with apparently normal karyotypes were found to belong to all sperm morphology classes. The number of morphologically abnormal sperms in two patients with karyotype anomalies of the XO/XY and XO/XY/XxO/XxY types was within normal limits. The third patient with an XO/XY mosaicism was found to belong to the class with 41–50% morphologically abnormal sperms. The two patients with Y chromosomes of unusual size had 31–40 and 41–50% morphologically abnormal sperms, respectively. Only one of the 3 patients with XY/XXY mosaicism produced any sperms at all and 41–50% of these were morphologically abnormal. The highest percentage of abnormal sperms associated with an aberrant karyotype, 51 to 60%, was found in the patient with a D/D translocation.

### *Histological Examination of Testicular Morphology*

Examinations of testicular morphology was carried out in 47 out of the 135 men belonging to this series. The individual observations concerning testicular morphology have been summarized in Table C of the Appendix. In order to analyse the relationship between mitotic karyotype and testicular morphology in this series of men, the relevant data have been presented in Table V.

All types of testicular lesions were found among patients with apparently normal karyotypes. Three patients with mosaicisms of different types, XO/XY; XO/XY/XxO/XxY and XY/XXY were found to have an apparently normal testicular morphology (Fig. 16). Four patients with XXY or XY/XXY sex chromosome constitutions had tubular sclerosis with severe reduction of the germinal epithelium and hyperplasia of the Leydig cells (Fig. 17). The 3 patients with different types of structural chromosomal aberrations or peculiarities, *e.g.* the patient with the D/D translocation, the patient with the delected Y chromosome and the patient with the very large Y chromosome, all had partial intratubular spermatogenetic arrest at the spermatid level (Fig. 18).

*Table V. Testicular morphology and mitotic karyotypes in 47 men attending an infertility clinic*

| Testicular morphology | No. of pat. | Karyotype interpretation | | No. of pat. | Case No. |
|---|---|---|---|---|---|
| **A. Testicular morphology without apparent signs of passed infection** | | | | | |
| Apparently normal testicular morphology | 23 | 46 | –XY normal | 20 | – |
| | | 45/46 | XO/XY | 1 | 6 |
| | | 45/46/47 | –XO/XxO/XY/XxY | 1 | 79 |
| | | 46/47 | XY/XXY | 1 | 115 |
| Slight to moderate impairment of spermatogenetic activity | 2 | 46 | XY normal | 2 | 25; 101 |
| Tubular sclerosis with severe reduction of germinal epithelium: | | | | | |
| 1—without Leydig-cell hyperplasia | 1+½ | 46 | –XY normal | 1 | 107 |
| | | 46 | –X + small y | ½ | (108–right test.) |
| 2—with Leydig-cell hyperplasia | 4 | 47 | –XXY | 2 | 120; 121 |
| | | 46/47 | XY/XXY | 2 | 55; 123 |
| Partial intratubular spermatogenetic arrest at the: | | | | | |
| 1—spermatid level | 3+½ | 46 | XY normal | 1 | 48 |
| | | 46 | –X + small y | ½ | (108–left test.) |
| | | 45 | XY–D/D: translocation | 1 | 110 |
| | | 46 | –X + large Y | 1 | 119 |
| 2—I spermatocyte level | 4 | 46 | –XY normal | 4 | 12; 42; 112; 124 |
| 3—spermatogonium level | 1 | 46 | XY normal | 1 | 99 |
| Germinal cell aplasia: | | | | | |
| 1—prepubertal type | ½ | 47 | –XY + extra minute chromosome | ½ | (85–left test.) |
| 2—postpubertal type or "Sertoli-cell-only" syndrome | 6+½ | 46 | –XY normal | 6 | 14; 27; 40; 53 |
| | | 47 | –XY + extra minute chromosome | | (85–right test.) |
| **B. Testicular morphology with apparent signs of passed infection** | | | | | |
| Interstitial and peritubular fibrosis in addition to tubular sclerosis with severe reduction of germinal epithelium (post mumps-orchitis) | 1 | 46 | –XY normal | 1 | 1 |

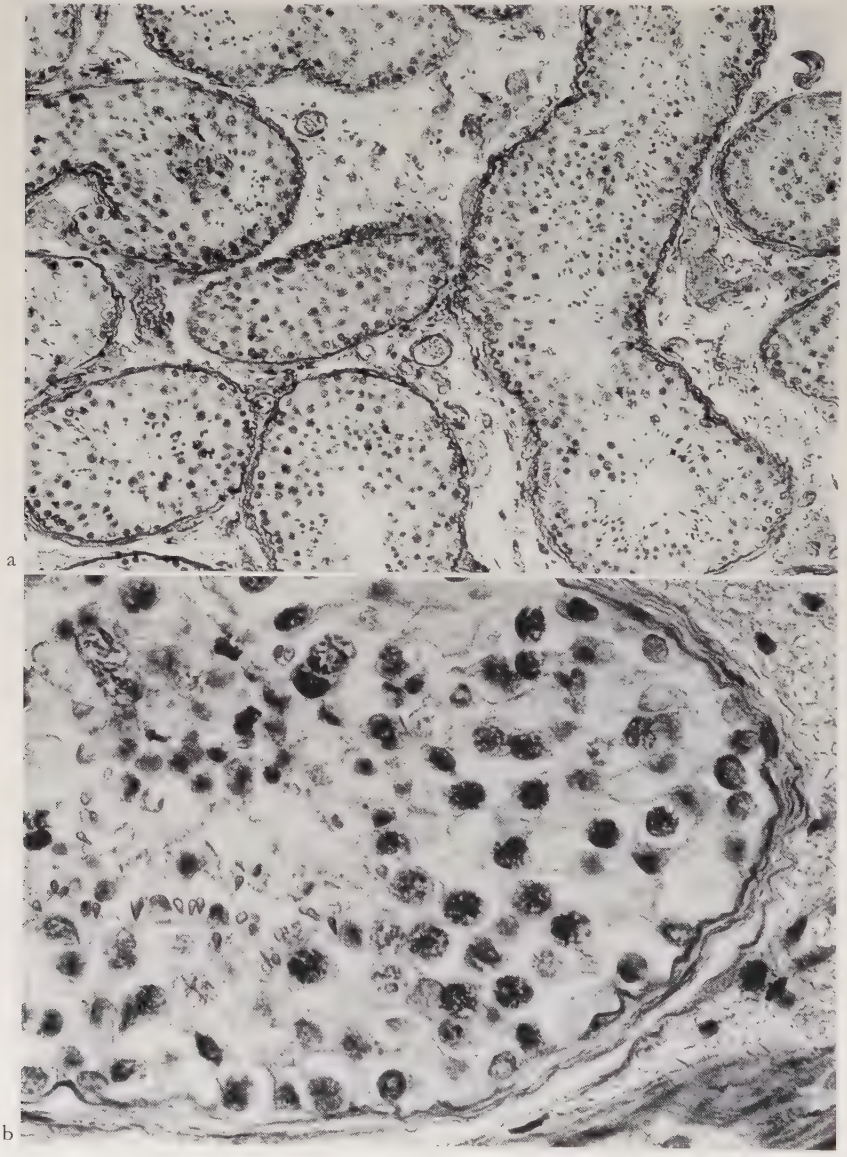



*Fig. 16. a)* Normal testicular morphology in a patient (case No.79) with 45/46/47 -XO/XY/XxO/XxY karyotype. – *b)* Normal testicular morphology in a patient (case No.115) with 46/47-XY/XXY karyotype. – Haematoxylin-eosin.

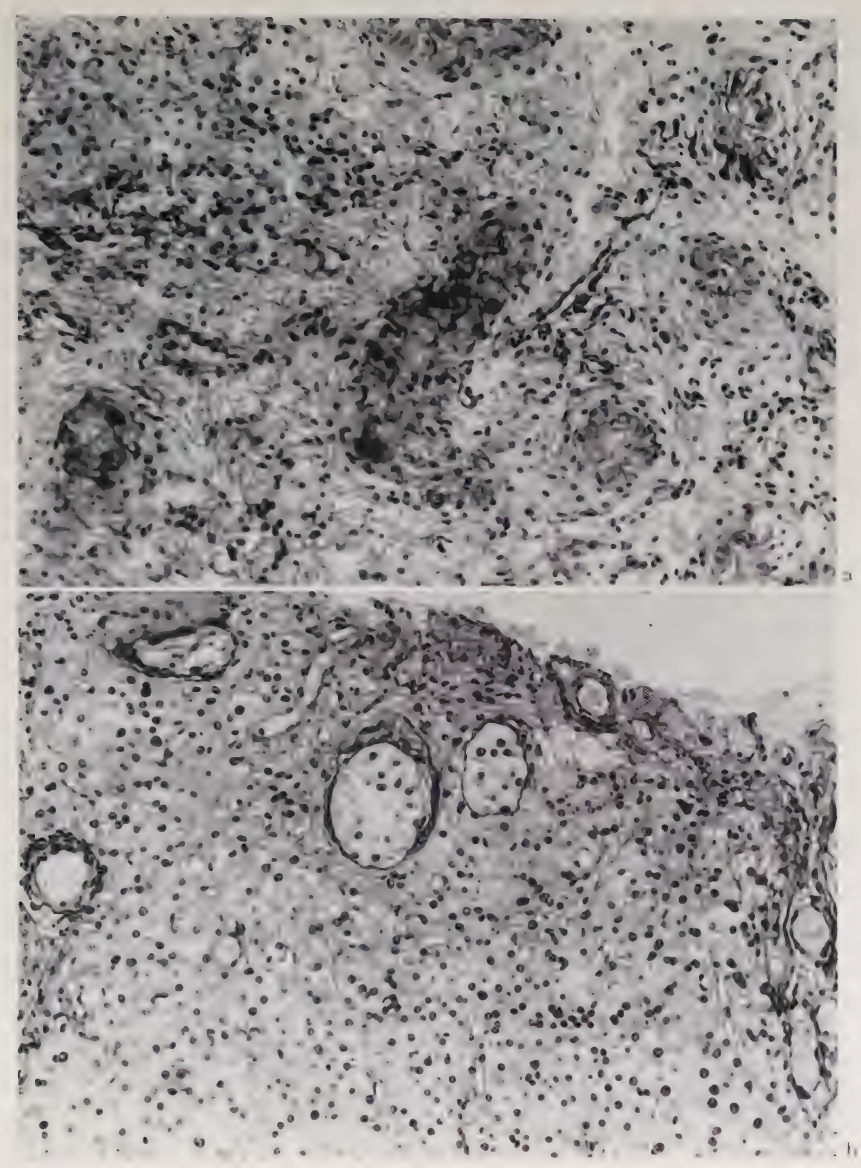


*Fig. 17. a*) Extensive tubular sclerosis, 'ghost tubules', in a sex chromatin positive male (case No. 120) with micro-orchidism (Klinefelter's syndrome) and 47/XXY karyotype. *b*) Extensive Leydig-cell hyperplasia together with 2 seminiferous tubules lacking germinal cells in a sex chromatin positive male (case No. 55) with micro-orchidism (Klinefelter's syndrome) and 46/47–XY/XXY karyotype. – Haematoxylin-eosin.

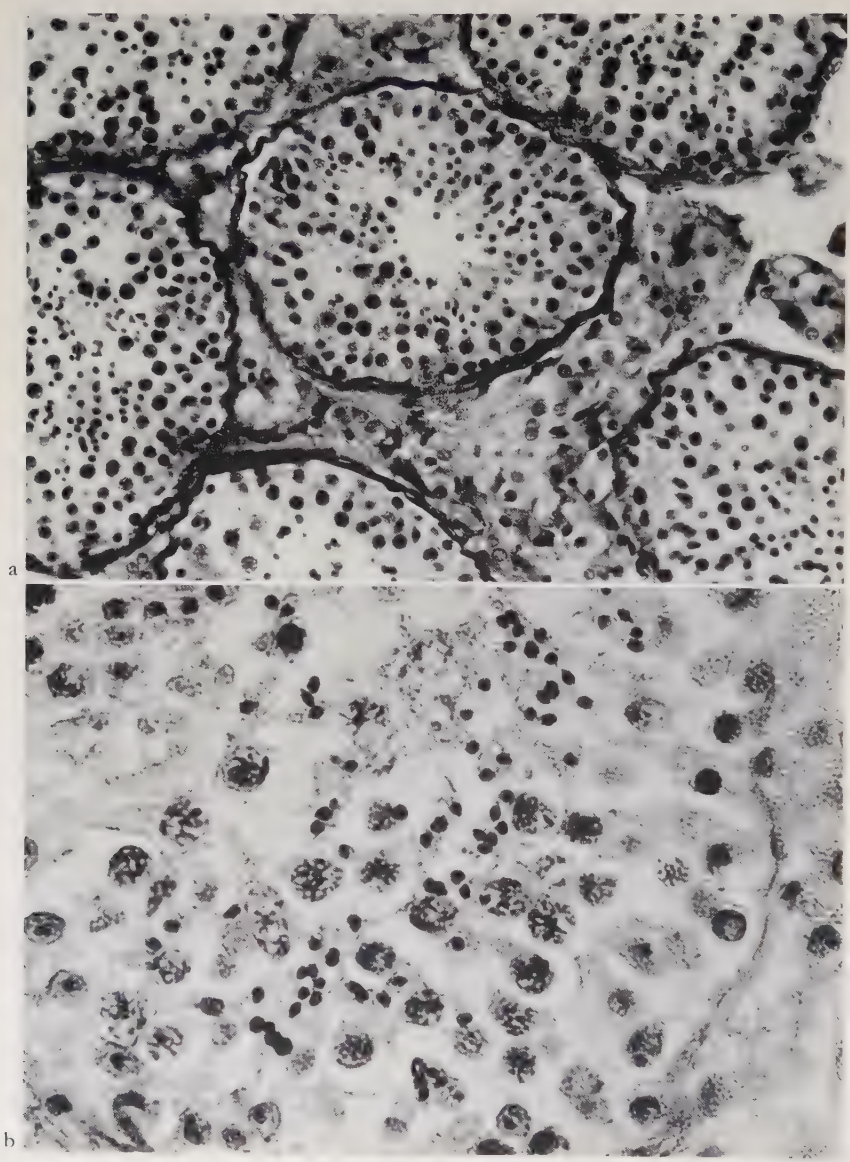


*Fig. 18. a*) Partial intratubular spermatogenetic arrest in a patient (case No.110) with a balanced D/D translocation. – *b*) Partial intratubular spermatogenetic arrest in a patient (case 108) with a possibly deleted Y chromosome. Degenerating germinal cells with pycnotic nuclei are seen towards the centre of the seminiferous tubule. – Haematoxylin-eosin.

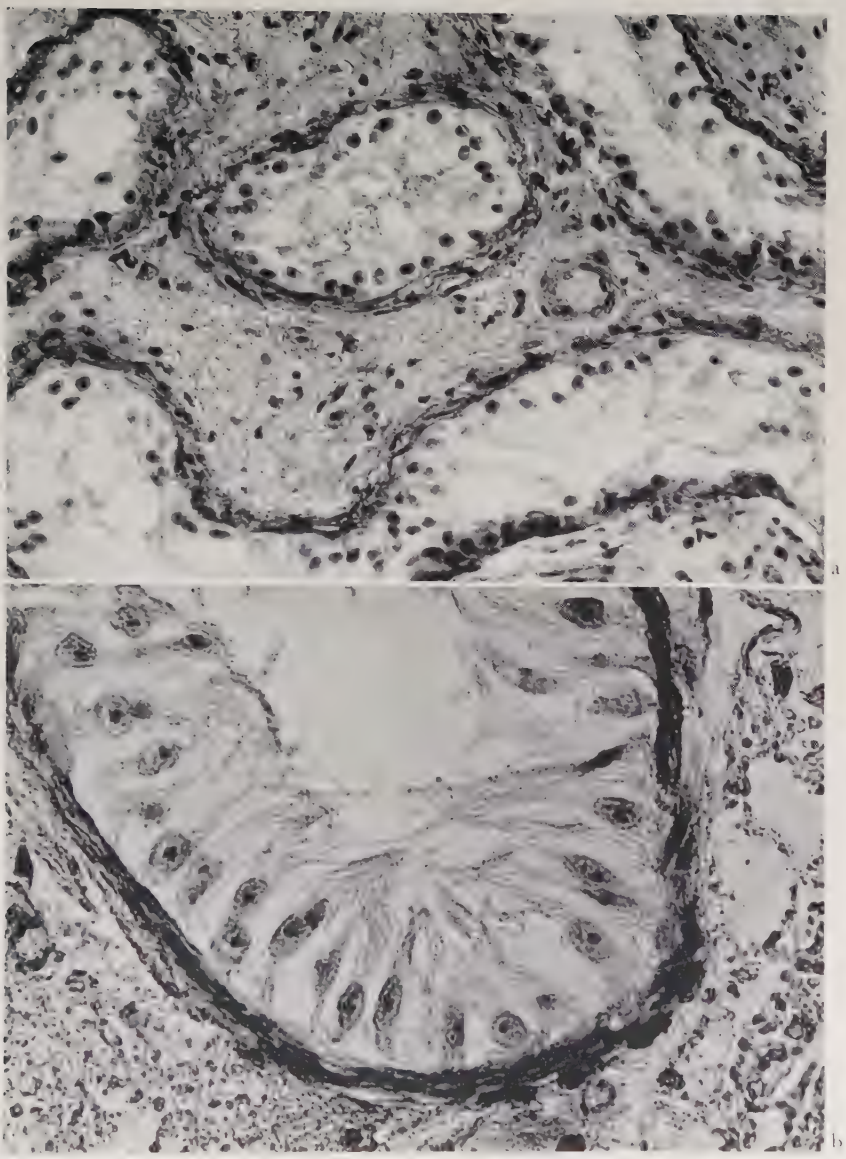


*Fig. 19. a*) Germinal cell aplasia (Case No. 14). - *b*) Germinal cell aplasia in a patient (case No. 85) with a supernumerary, minute and metacentric chromosome of possible sex chromosomal origin (right testicule). – Haematoxylin-eosin.

Germinal cell aplasia was recognized in 7 patients (Fig. 19). Six of these had apparently normal karyotypes and one had a supernumerary 47th chromosome of possibly sex chromosomal origin. Histological examinations were made of testicular biopsy specimens from both sides of case No. 85, the patient with the supernumerary chromosome. The germinal cell aplasia was found to be of the prepubertal type on the left were the testicle was originally undescended, whereas on the right side, the findings were consistent with the post pubertal 'Sertoli-cell-only' syndrome in a fully descended testicle.

## *Clinical Investigations*

All clinical observations and data concerning individual patients have been summarized in Tables A and D of the Appendix. On admission, the average age of the 135 men included in this series was 30.5 years, ranging from 19 to 48 years. The mean duration of the current period of involuntary childlessness at the same time was 4.4 years, ranging from 16 years to 6 months. From Table VI, it is seen that only one of the patients with a deviant karyotype, a mosaic of the XO/XY/XxO/XxY type had a history of a previous conception, but this ended in a spontaneous miscarriage. Other patients with chromosome aberrations reported that no conceptions at all had occurred or even been suspected (Table VI).

Extended clinical investigations were carried out in the 12 patients with deviating karyotypes and the relevant data are presented in Table D of the Appendix. Four out of the 5 patients with the XXY or XY/XXY sex chromosome constitution were found to have smaller and somewhat softer testes than normal. Only one sex chromatin positive patient displayed the classical clinical symptoms consistent with the Klinefelter's syndrome. The other sex chromatin positive males, who also had cells with the XXY sex chromosome constitution, did not display such distinct clinical features on physical examination. Two of the sex chromatin positive patients were sexually impotent. A penile malformation was found in only one patient, case No. 108. He had a possibly delected Y chromosome together with hypospadias. The 3 patients with XO/XY and XO/XY/XxO/XxY mosaicism respectively were all found to be normal on physical examination.

*Table VI. Previous conceptions and mitotic karyotypes in 135 men attending an infertility clinic*

| Without previous conception | | | | With previous conception | | |
|---|---|---|---|---|---|---|
| No. of regular partners | History of previous conception | Karyotype interpretation | No. of patients | History of previous conception | Karyotype interpretation | No. of patients |
| | 0 | 46/XY normal | 102 | + | 46/XY–normal | 5 |
| | 0 | 47/XXY | 2 | ✦✦✦ | 46/XY· normal | 3 |
| | 0 | 47/XY+extra | 1 | ✦✦ | 46/XY–normal | 4 |
| 1 | | minute metacentric chromosome | | ✦ | 46/XY–normal | 6 |
| | 0 | 46/47–XY/XXY | 3 | ✦ | 45/46/47 · XO/XY/XxO/XxY | 1 |
| | 0 | 45/46–XO/XY | 2 | | | |
| | 0 | 46/X–small y | 1 | | | |
| | 0 | 46/X–large Y | 1 | | | |
| 2 | 0/0 | 45/XY D~D | 1 | + + /0 | 46/XY–normal | 1 |
| | | | | + /0 | 46/XY–normal | 1 |
| 3 | | | | +/+/0 | 46/XY–normal | 1 |

0 = apparently no previous conception
✦ = miscarriage
+ = normal living child

/ = signs on any one side of the bar refers to one and the same regular partner

# DISCUSSION

## *Karyotype, Testicular Morphology and Spermatogenesis*

The incidence of chromosomal anomalies in randomly selected men and women has been studied by JACOBS *et al.* (1964) and COURT-BROWN *et al.* (1965). Among 207 men analysed, they found 1 carrier of a balanced translocation between 2 autosomes and 1 individual with a structurally altered Y chromosome, possibly with an inversion, together with 6 individuals with normal autosomal 'variants' and 4 with an unusual length of the Y chromosome. They estimated that 0.5% of adults have chromosomal structural rearrangements and that about 3% of males have Y chromosomes of an unusual size.

In the present series of 135 consecutively analysed men attending an infertility clinic, regardless of their fertility, 10 were found to have an aberrant karyotype and 2 to have an unusual size of their Y chromosome.

FERGUSON-SMITH *et al.* (1957), in a sex chromatin survey of 96 sterile men attending a male subfertility clinic, found 10 of them to be sex chromatin positive. No karyotype analyses were carried out. The incidence of chromatin positive males among all subfertile men attending the same subfertily clinic was estimated to be between 1 and 3%, and if only men with a sperm count of less than 1 million sperms per ml were considered, the incidence was found to be about 11%.

Occasional individuals with an unusual size of the Y chromosome and oligospermia or aspermia have been described by van WIJK *et al.* (1962, 1963), DE LA CHAPELLE and HORTLING (1963), MAKINO *et al.* (1962), MAKINO and MURAMOTO (1964). There are, however, no previous publications on systematical, cytogenetical investigations on male partners in barren marriages. In agreement with the observations of FERGUSON-SMITH *et al.* (1957), the incidence, in the present series, of sex chromatin positive males with less than 1 million sperms per ml was 16%, a total of 4 individuals. These 4 patients could all be classified in the clinical category of sex chromatin positive micro-orchidism according to the terminology suggested by FERGUSON-SMITH (1959).

However, only 2 of them had the usual XXY sex chromosome constitution, whereas the other 2 were interpreted as chromosomal mosaics of the XY/XXY type. A third case with the same type of XY/XXY mosaicism was neither sex chromatin positive nor did he have microorchidism. Sperm analyses showed that all chromatin positive individuals lacked sperms in their ejaculates. Moreover, all of them also lacked histological signs of spermatogenesis. This is in agreement with the usual findings in individuals with chromatin positive Klinefelter's syndrome. The third case of XY/XXY mosaicism, however, not only produced some sperms, but also had normal testicular morphology. As the proportion of XXY cells in the latter case was rather small compared to the other two cases, it seems reasonable to assume that the proportion of XXY cells in the primitive gonad is a decisive factor in subsequent gametogenesis (Court-Brown *et al.*, 1964). Analysis of meiotic chromosomes in primary spermatocytes at diakinesis and metaphase I in the case with a low proportion of XXY cells, failed to show spermatocytes with an extra X chromosome. This might have been due to chance, or it could be that cells with an XXY sex chromosome constitution do not enter meiosis. The latter explanation is in agreement with the observations in prepubertal sex chromatin positive boys made by Ferguson-Smith (1959) who found that the majority of germinal cells usually degenerate at prepubertal ages and before meiosis begins.

Fertility in a sex chromatin positive male with an XY/XXY mosaicism was reported by Court-Brown *et al.* (1964b), and was also claimed by Warburg (1963) for a sex chromatin positive male with Klinefelter's syndrome, who 'possibly represented a mosaic of the XXY/XY type with a marked preponderance of the former cell type'.

Dowling and Knox (1963) reported fertility in a sex chromatin negative male with XY/XXY mosaicism, who had a total of 84 million sperms per ml in the one sample of semen analysed. Complete spermatogenesis was also observed by Barr *et al.* (1962) in cut sections of testicular tissue which were shown to include cells of the XY and XXXY types. So far, fertility does not seem to have been conclusively proven in individuals with a pure XXY sex chromosome complement, while some reports indicate that gametogenesis may occur in gonads which include a sufficient amount of normal XY cells along with aberrant cells of the XXY or even XXXY types. These mosaic individuals may or may not have features characteristic of Klinefelter's syndrome and may be sex chromatin positive or negative. The only satisfactory method of identification thus seems to depend on karyotype analysis.

The effect of chromosomal mosaicism of the XY/XXY type on fecundity and subsequent fertility in the human male thus seems to be closely related to the proportion of normal XY cells to aberrant XXY cells in the gonads. So far, the observations on such individuals are too scanty to decide how the aberrant cells influence fecundity but it seems likely that in these individuals the XY germ cells only enter meiosis and are capable of producing mature sperms, while the aberrant germ cells are eliminated early during spermatogenesis. Proven paternity in a number of such cases together with observations on testicular morphology and meiotic chromosomes as well as sperm analyses are all in agreement with such an assumption. Fecundity and fertility may thus be impaired due to this mosaicism because of a reduction in the number of mature and normal gametes produced and this will in turn be dependent on the amount of aneuploid spermatogonia present in the primitive gonad.

Aspermia, due to germinal cell aplasia, was found in one case, No. 85, together with an aberrant karyotype including a supernumerary metacentric chromosome comparable in size with the members of the G or 21–22 group. One testicle was undescended but extra-abdominally situated. The other testicle was normal in position, shape and consistency. The patient had no other abnormalities. The origin of the supernumerary chromosome could not be established by its morphological features or by labelling with tritiated thymidine. The patient was sex chromatin negative which is evidence against an X chromosomal origin of the extra chromosome. However, deletions may occur in both arms of an extra X chromosome which could leave a minute X chromosome consisting of the most central parts of the original chromosome only. The remaining X chromosome material might then be too small to give rise to a detectable sex chromatin body. Another explanation is a structural rearrangement of a Y chromosome, such as pericentric inversion, which would agree with the absence of a sex chromatin body in interphase nuclei. Extra Y chromosome material does not necessarily interfere with the somatic development or fertility of the carrier (SANDBERG *et al.* 1961, 1963). However, SANDBERG *et al.* (1963) drew attention to a possible tendency for an association between testicular non-descent and an extra Y chromosome. FRØLAND *et al.* (1963b) and GUSTAVSON (1964) described two boys with karyotypes including an extra chromosome, similar to the present one, who displayed various congenital malformations and mental retardation. In those cases, the extra chromosome was tentatively interpreted as of autosomal origin,

an interpretation which has been considered less likely in the present case because of a lack of severe somatic or mental maldevelopment. The aetiology of the clinical syndrome 'germinal cell aplasia' has been a matter of speculation. In their original description of the syndrome, Del Castillo *et al.* (1947) suggested a genic factor controlling the migration of primordial germ cells as the cause of the histological defect. In the male mouse embryo, Minz (1960a and b) showed that reduction or inhibition of this migration of primordial germ cells to the primitive gonadal ridges could be caused by a mutant gene. The final result was testicular histology consistent with the findings in patients with germinal cell aplasia. Chromosome studies have occasionally been performed on patients with germinal aplasia, but most of them had normal karyotypes (Solari *et al.*, 1963; Valencia *et al.*, 1963 and Ferguson-Smith *et al.*, 1963).

In the present series, apparently normal karyotypes were found in 6 out of 7 individuals with this syndrome. Recently however, De la Chapelle *et al.* (1964), Therkelsen (1964a and b) and Ferguson-Smith (1965) have reported phenotypical males with germinal cell aplasia in at least one testis and an apparently normal female karyotype. Mosaicism, however, can not be definitely excluded in such cases. The same testicular histology has also been recognized in individuals with gonadal dysgenesis of an only apparent testicle, the second gonad being either absent or intra-abdominal. These individuals were shown to be mosaics of the XO/XY type by De la Chapelle and Hortling (1962), Ferrier *et al.* (1963) and Ross *et al.* (1965). At present it should be safe to conclude that the syndrome of germinal cell aplasia may sometimes occur in association with chromosomal aberrations of different types and that some observations suggest an influence of specific genic factors.

As yet, about 30 cases of apparent XO/XY mosaicism have been reported. The majority of these patients had a female phenotype and only 8 were raised as males. All men with XO/XY mosaicism reported so far have been sterile because of gonadal dysgenesis and all individuals described were found to have only one detectable gonad after puberty. In contrast to these observations, this series includes 2 cases of XO/XY mosaicism and 1 case of probable XO/XY/XxO/XxY mosaicism, with apparently normal reproductive organs. Compared to the other patients in this series who had karyotype anomalies and active spermatogenesis, these 3 patients proved to have a superior sperm production. Earlier observations of some form of gonadal dysgenesis

in all male cases of XO/XY mosaicism as reviewed by ROBINSON *et al.* (1964), MAKINO *et al.* (1964), FERGUSON-SMITH (1965) and others could be explained by special selection of cases for analysis. The effect of XO/XY mosaicism on the fertility of men who retain spermatogenesis, depends on the types of gametes that they may produce. In this series, 1 patient with XO/XY mosaicism and another with XO/XY/XxO/XxY mosaicism apparently had primary spermatocytes with an XO sex chromosome constitution. They had no histological signs of intratubular spermatogenetic arrest or germinal cell degeneration. Sperm analyses showed an average count of over 20 million sperms per ml and a frequency of morphologically abnormal sperms which varied between 26 and 49%. Theoretically, 2 types of gametes are to be expected in equal proportions, from XO spermatocytes: sperms carrying the haploid set of autosomes and one X chromosome and those carrying the haploid set of autosomes only. It is agreed that X and Y bearing sperms cannot at present be separated by their morphological characteristics (BISHOP, 1960; VAN DUIJN, 1961). Furthermore, it has been shown by LINDSTEN (1963) that some patients with Turner's syndrome and an XO sex chromosome constitution have inherited their only X chromosome from their mother. This implies either fertilization of an ordinary X bearing ovum by a sperm lacking a sex chromosome or zygotic misdivision with subsequent loss of the paternal sex chromosome at the first cleavage after fertilization. The first alternative appears more likely. Thus it seems that spermatids without a sex chromosome may develop into mature sperm of normal appearance and capable of fertilization. At present, sperm analyses or clinical examination do not provide any criteria on which to base a diagnosis of XO/XY mosaicism. Such patients can only be identified by karyotype analysis, preferably supplemented by meiotic chromosome analysis. The reproductive implication of a paternal XO/XY mosaicism depends on the number of XO zygotes produced by fertilization of ordinary ova with sperms lacking a sex chromosome.

According to TWIESSELMANN *et al.* (1962) 'the Turners (XO) of paternal origin are twice more frequent than those of maternal origin, if we admit that the probabilities of both segregation and non-disjunction are equal in both sexes'. In paternal mosaicism of the XO/XY type, this ratio is likely to increase to an extent which will depend on the proportion of XO spermatogonia present in the male gonads. A recent investigation of karyotypes of aborted embryos by CARR (1965) showed that X monosomy was the prevalent chromosome anomaly with an

incidence of 5.5%. Only 1 in 40 XO zygotes is assumed to survive to term. Consequently a paternal mosaicism of the XO/XY type is likely to increase the risk of spontaneous abortions due to production of XO zygotes.

The Y chromosome is known to vary considerably in length. Usually the Y chromosome can be included in the G or 21–22 group, by its length and morphological features (the Denver system for classification of human mitotic chromosomes, 1960). There are several reports on the association of different malformations with variations in length of the Y chromosome (see reviews by MAKINO and MURAMOTO, 1964; GRIPENBERG, 1964 and COURT-BROWN *et al.*, 1964a). Large variations in size from less than ½ the length of an ordinary G (21–22) group chromosome to about the size of a D (13–15) group chromosome have been regarded as within normal limits for this particular chromosome. In a series of 29 patients with oligospermia or aspermia, not including patients with the Klinefelter's syndrome, VAN WIJK *et al.* (1963) found 3 patients with a very large Y chromosome and 1 patient with a remarkably small Y chromosome. Occasional cases with aspermia or severe oligospermia associated with Y chromosomes of unusual size have been described by DE LA CHAPELLE *et al.* (1963), WENNSTRÖM and DE LA CHAPELLE (1963), MAKINO and MURAMOTO (1964) and MAKINO (1964).

Unusual length of the Y chromosome has also been shown to be a heritable trait (BENDER and GOOCH, 1961; BISHOP *et al.*, 1962; DE LA CHAPELLE *et al.*, 1963). Since several normal male relatives of the propositi were shown to be carriers of the same trait, an abnormally long Y chromosome does not appear to exert any influence on physical development or reproductive capacity. There are however very few reports on gametogenesis in males with deviations of their Y chromosomes.

The incidence of Y chromosomes of unusual length in randomly selected adult men have been estimated to be about 3% (COURT-BROWN *et al.*, 1965).

A very small Y chromosome, possibly deleted, was reported by MULDAL and OCKEY (1961) in a father and his 2 sons who all had mild hypospadias. The fertility of one of the carriers, the father, obviously was not decreased. MAKINO *et al.* (1964) found a large Y chromosome in one out of 3 additional individuals displaying hypospadias. In the present series, 1 patient had a very small, possibly deleted Y chromosome in all cells analysed together with hypospadias, unilateral partial cryptorchidism and severe oligospermia. The patient was an only child

and the parents had been married for some years before pregnancy occurred. The father was deceased but the paternal uncle, who also had a history of involuntary childlessness, also carried a similar small Y chromosome. If this, possibly deleted, Y chromosome is a heritable trait, it would imply that the paternal grandfather of the patient was a fully fertile carrier of the small Y chromosome as he obviously was the last common ancestor of the recognized carriers.

Another patient belonging to this series, had a very large Y chromosome sometimes indistinguishable from an ordinary D (13–15) chromosome. His father and brother were not available for chromosome analysis. The consequences of Y chromosomes with unusual size on male fecundity and fertility merit further inquiry. VAN WIJK *et al.* (1963) suggest that observation of varying lengths of the Y chromosome in apparently normal individuals does not necessarily exclude the possibility that this peculiarity is pathogenic.

Since the first suggestion was made by BELLING (1925) that inherited reduced fertility might be due to the special pairing and segregation of structurally interchanged chromosomes during the first meiotic division, this hypothesis has often been confirmed through genetical as well as cytological investigations. SNELL (1933 a and b) showed that offspring of irradiated mice could become 'semi-sterile' due to structural rearrangements of the chromosomes, such as reciprocal translocations. This reduced fertility was also shown to be associated with non-viable zygotes due to the formation and fertilization of unbalanced gametes resulting from abnormal pairing, segregation and separation of structurally altered chromosomes during the first meiotic division (DARLINGTON, 1931, 1937 and SWANSON, 1960).

In man, structural heterozygosity, detectable by examination of mitotic metaphase chromosomes, has been reported in about 0.5% of randomly chosen men and women (COURT-BROWN *et al.*, 1965). The usual way to ascertain carriers of balanced reciprocal translocations has been through the study of families of index cases carrying an unbalanced chromosome set causing a significant phenotypical abnormality. Sometimes the structural heterozygotes have been found in investigations of families with repeated miscarriages. There have been no reports on systematical, cytogenetical investigations concerning the prevalence and fertility of balanced reciprocal translocation carriers in barren marriages.

Balanced states of translocation heterozygosity are known to have been transmitted through several generations by phenotypically normal

female as well as male carriers (Walker and Harris, 1962a and b; Oikawa *et al.*, 1962; Lejeune *et al.*, 1963; Zergollern *et al.*, 1964; Yunis *et al.*, 1964; Uchida *et al.*, 1964; Lindsten *et al.*, 1965).

The reproductive capacity of a balanced male translocation heterozygote is closely related to the number and proportion of balanced to unbalanced gametes produced. These factors are in turn dependent on the pairing and segregation of the structurally altered chromosomes and their homologous partners during first meiotic prophase and metaphase.

In the present series, a phenotypically normal D/D translocation heterozygote was identified among the patients with a low sperm count and many morphologically abnormal sperms. The trivalent observed at diakinesis and metaphase I had a morphology consistent with what could be expected with respect to the size of the chromosomes involved in the translocation (Fig. 9c). In a translocation heterozygote of this constitution, 2 main types of gametes are likely to be produced: one type carrying a genetically balanced set of chromosomes and another carrying an unbalanced set (Fig. 9c). There are of course several ways in which the distribution of the chromosomes on the daughter cells could occur at first meiotic anaphase giving rise to many different types of unbalanced gametes. Secondary spermatocytes at metaphase should be a suitable type of cell for the study of the result of the segregation of chromosomes. However, cells in these stages are not very often seen, and when found they are usually not of a sufficient technical quality for appropriate examination. So far, few reports have been published on the behaviour of structurally changed human chromosomes during meiosis. The first report by Hamerton *et al.* (1961) described a male carrier of a balanced translocation between one large and one small acrocentric chromosome belonging to the D (13–15) and G (21–22) groups respectively. A trivalent configuration was observed at diakinesis and metaphase I in cytological preparations from testicular biopsy. In addition to the present case, another two reports on meiosis in male carriers of balanced translocations have been published by Polani (1964) and Lindsten *et al.* (1965).

The consequence of a balanced D/D translocation, or alternatively a centric fusion D–D, for the fertility of male heterozygotes has been discussed by Stalder *et al.* (1965).

At present a total of 11 male carriers, or probable carriers of a D/D chromosome who have reached sexual maturity, have been reported including the present case (Cooper and Hirschhorn, 1961; Walker

and HARRIS, 1962a and b; OIKAWA *et al.*, 1962; KJESSLER, 1964; ZERGOLLERN *et al.*, 1964; and YUNIS *et al.*, 1964).

As data on fertility was not reported for the patient described by COOPER and HIRSCHHORN (1961), 10 men only can be considered. Two of them were clinically sterile (KJESSLER, 1964; YUNIS *et al.*, 1964). The remaining 8 men had produced offspring. Four of them each had 1 child, 1 had 2, 2 had 3, and 1 had 4 children. Considered otherwise, this implies that 20% of all male D/D translocation heterozygotes who had reached sexual maturity displayed clinical sterility whereas 40% had only one child and 40% of these men had 2 or more children. Eight of these 10 men had fathered a total of 22 pregnancies, 6 of which had ended in spontaneous miscarriages, but 5 of these abortions recurred in the same marriage. Among the 16 children of the 8 male translocation heterozygotes, there was one with the characteristic signs and symptoms of Down's syndrome. Karyotyping confirmed trisomy 21 in this child but at the same time the patient was a balanced carrier of a D/D translocation. The remaining 15 children were all phenotypically normal, 6 of them with normal karyotypes, a further 6 were balanced carriers of the translocation chromosome and 3 were not studied cytogenetically. While these results rule out the existence of karyotypes with effectively a trisomy of the D group chromosomes among the surviving children, such trisomies may have existed in one or more of the aborted embryos or in zygotes that did not nidate. The frequency of spontaneous abortions in these unions does not, however, seem to be raised. Moreover, in the spontaneous abortion material analysed by CARR (1965), no fetuses with a monosomy D or trisomy D of the translocation type were discovered. These observations suggest that only sperms which are balanced with respect to their D chromosomes have been efficient at fertilisation.

In cases of D/G and D/D translocations, HAMERTON *et al.* (1961), SHAW (1962), HAMERTON and STEINBERG (1962) and MACINTYRE *et al.* (1962) suggested that preferential segregation influenced the proportions of normal haploid sperms to those carrying the translocation chromosome in balanced combination and those with different types of unbalanced chromosome combinations. Cytologically, different classes of sperms produced by male carriers of balanced translocations were also thought by HAMERTON *et al.* (1961) to vary in their efficiency at fertilizing ova, so that not only preferential segregation but also selective fertilization in favour of balanced sperms would occur. In this patient the number of ejaculated sperms was severely reduced and about

50% of these were morphologically abnormal. In the present D/D carrier, the finding of a partial intratubular spermatogenetic arrest might reflect an early intratubular elimination of unbalanced gametes (Fig. 18a).

Further investigations on gametogenesis in male D/D translocation heterozygotes are needed before certain conclusions about the influence of the D/D translocation chromosome on gametogenesis can be drawn.

At present, it may only be stated that the main effect of the D/D chromosome on the fertility of its carrier is likely to be a reduced production of normally functioning sperms.

### *Chromosomal Behaviour at Diakinesis and Metaphase I*

Much of our knowledge about the structure and behaviour of human meiotic chromosomes at diakinesis and metaphase I in the male stems from an investigation by Ford and Hamerton (1956). These investigators reported that in 23 primary spermatocytes derived from 3 men, the X and Y chromosomes appeared connected 'end-to-end' in about 86% of the cells and were separated in about 14%. Different frequences of cells with free sex chromosomes at diakinesis and metaphase I have been reported, *i.e.* about 40% by Kodani (1958) and 27% by Sasaki and Makino (1965). In this material the X and the Y chromosomes were observed as free univalents in only 4.4% of the cells analysed. The difference between the present figure and those of the above mentioned investigators could be explained by differences in the chromosome preparation techniques used.

Precocious separation of the sex chromosomes during first meiotic division in man was observed by Painter (1923) and Koller (1937) in cut sections of testicular tissue where the chromosome orientation on the spindle is preserved. However, observation of the sex chromosomes in squash or air preparations as free univalents could just as well be due to non-association of the sex chromosomes as to precocious disjunction or technical errors. It has been suggested that a common cause of sex chromosomal aneuploidy is the presence of univalent sex chromosomes and their consequent random distribution at anaphase I. However, the low frequency of cells with free sex chromosomes observed in this material does not support this view.

The frequency of associated and free sex chromosomes respectively did not vary appreciably between individuals with different karyotypes (see Table B 1 of the Appendix).

Detailed analysis of the sex bivalent in several hundred cells failed to provide any cytological evidence for presence of a real chiasma between the sex chromosomes, which is consistent with earlier observations (SACHS, 1954 and SASAKI and MAKINO, 1965). As the true nature of this terminal association between the X and Y chromosomes is undecided, it has not been classified as a chiasma in this work.

HUSKINS and HEARNE (1936), working on male mice, showed that the pairing of homologous autosomes and chiasma formation between them is genetically controlled with variations between different strains of animals.

CREW and KOLLER (1932) reported higher chiasma frequencies and crossing over values in female mice than in males. SLIZYNSKI (1955) showed that the distribution of chiasmata per bivalent varied in male mice with the genetic constitution of the animal.

In this material, the average number of chiasmata per cell for the 25 men with apparently normal karyotypes was 52.7. This is lower than the frequency of 55.9 per cell found in 3 men reported by FORD and HAMERTON (1956). At present, it is not possible to say whether or not this discrepancy is suggestive of any biological differences. It could be explained by differences in the stages of first meiotic division at which the 2 samples of cells were examined. No fertility data were reported by FORD and HAMERTON (1956). More extensive and detailed data are needed in order to analyse the correlation between chiasma frequency and fertility in the human male.

A significantly lower chiasma frequency of 47.0 per cell was recorded for the patient that was a D/D translocation heterozygote. It is possible that the presence of the translocation chromosome and the formation of trivalents interferes with the dynamics of the other chromosomes so as to cause a general reduction of chiasma frequency.

On theoretical grounds, one must assume that sperms are subject to genetical variation affecting metabolism as well as morphology. According to HOLLANDER *et al.* (1960) genic factors must exert their influence on the diploid primary spermatocyte in order subsequently to cause a defect of acrosomal development with altered sperm morphology as the end result. The haploid genotype of the spermatid, or the gamete itself, was not thought to have any influence on sperm morphology. On the other hand, it was claimed by BEATTY (1958) and BISHOP (1960), 'that, although not conclusive, the evidence that segregated genes may affect the phenotype of mammalian spermatozoa is at least highly suggestive'.

However, the fact that the present investigation has not contributed to

the clarification of these problems may indicate that the classification of the abnormalities of sperms which is used for clinical purposes is inadequate for a genetical investigation.

The high frequency of morphologically abnormal sperms produced by the patient with a D/D translocation might suggest that these abnormalities could be associated with unbalanced haploid chromosome sets. It is however not possible to prove such an assumption as yet.

No clearcut associations were found between testicular histology and different sorts of karyotype deviation, except in some of the sex chromatin positive patients with micro-orchidism and seminiferous tubule dysgenesis or Klinefelter's syndrome. Other types of testicular spermatogenetic deficiency were not associated with karyotype variations in this material. For this reason, and others mentioned below it is therefore desirable to include karyotype analysis and meiotic studies in the investigation of cases of male infertility.

With the exception of the clearcut cases of Klinefelter's syndrome, which may be chromatin positive, clinical examinations do not give any clear indications as to which patients might have a deviate karyotype. Furthermore, in the present series, somatic, mental and particularly sexual development was not appreciably different in individuals with apparently normal karyotypes as compared to those with different types of chromosome anomaly.

# SUMMARY

The aim of the present investigation has been to examine a consecutive series of men attending an infertility clinic with respect to mitotic karyotype, the structure and behaviour of the meiotic chromosomes in primary spermatocytes during diakinesis and metaphase I, serial analyses of sperm count and sperm morphology and testicular histology. Relevant clinical data concerning the current period of involuntary childlessness were also considered and included family, social and previous medical history.

The patients were referred to the Infertility clinic and admitted without regional restrictions.

No consideration was given to the gynaecological findings in the female partners or the actual fecundity of the males. The material may not represent a true random sample from the universe of barren marriages since several patients were referred subsequent to examinations elsewhere.

Mitotic karyotype analyses were carried out in cultured leucocytes and cultured fibroblasts derived from skin and testicular biopsy specimens. Meiotic chromosome preparations were made according to a special technique described in same detail. Serial analyses of sperm count and sperm morphology were made in each patient. Testicular morphology was examined in cut sections of testicular biopsy specimens prepared according to routine techniques. All patients were asked about previous conceptions as well as the duration and other relevant details about the current period of involuntary childlessness. The patients who agreed to testicular biopsy had a complete clinical examination and their history was supplemented by questions about their physical, mental and sexual development as well as about their, family, social and previous medical history.

During the year between April, 1st, 1964 to March, 31st, 1965 135 patients were examined. Ten patients had abnormal karyotypes and 2 had Y chromosomes of unusual size. The remaining 123 patients all had apparently normal karyotypes, with due reservations about possibly undiscovered cases of mosaicism.

The incidence of patients with sex chromatin-positive micro-orchidism, or Klinefelter's syndrome, was found to be 16% in men with less than 1 million sperms per ml belonging to this series. Two of these patients were found to have an XXY sex chromosome constitution and 2 had mosaicism of the XY/XXY type. One sex chromatin negative patient without the clinical or histological stigmata of Klinefelter's syndrome also had a chromosomal mosaicism of the XY/XXY type. Sperm analyses showed all the sex chromatin positive patients to have no sperms in their ejaculates, while the sex chromatin negative XY/XXY patient produced sperms.

Germinal cell aplasia was revealed in 7 patients with aspermia. One of these had a supernumerary, minute and metacentric chromosome of possibly sex chromosomal origin, while the others had apparently normal karyotypes.

Chromosomal mosaicism of the XO/XY type, associated with a male phenotype, was found in 2 patients. A similar but somewhat more complex mosaic of the XO/XY/XxO/XxY type was found in one other patient who had a marked preponderance of cells of the XO and XY types. These 3 patients all had apparently normal reproductive organs together with a fair spermatogenetic capacity. This is contrary to previous reported findings.

The Y chromosome was shown to be of unusual size in 2 patients. A very small, possibly deleted, Y chromosome was associated with hypospadias, unilateral cryptorchidism and severe oligospermia in one patient. Another patient with oligospermia was shown to have a large Y chromosome, sometimes indistinguishable from an ordinary D or 13–15 group chromosome. There was no definite evidence about the effect of Y chromosomes of unusual size.

An autosomal structural rearrangement of the translocation type was disclosed in one patient with clinical sterility. Mitotic karyotype analysis, together with meiotic chromosome studies, provided evidence for the presence of a translocation between 2 heterologous D group chromosomes. It was shown that a trivalent was formed in all primary spermatocytes analysed at diakinesis and metaphase I. The total number of chromosomal elements in such spermatocytes never exceeded 22.

A total of 550 primary spermatocytes at diakinesis and metaphase I from 25 men with apparently normal karyotypes, belonging to the present series, were examined with regard to the number of chiasmata per cell and the distribution of chiasmata per bivalent. The average chiasma frequency per cell was found to be 52.7. The average chiasma

frequency per cell in a D/D translocation heterozygote was significantly reduced, or 47.0 per cell. The autosomal structural rearrangement was thought to exert an interchromosomal influence with reduced chiasma frequency in general as the result. Patients with sex chromosome anomalies of different types did not differ from patients with apparently normal karyotypes with regard to average chiasma frequency per cell.

The distribution of chiasmata per bivalent was examined in 29 individuals with different karyotypes. In 25 men with apparently normal karyotypes who belonged to this series, 16.2% of the bivalents had a single chiasma, whereas 39.7 and 33.4% of the bivalents had 2 and 3 chiasmata respectively. Four chiasmata were found in 9.6% of the bivalents and 1% had 5 chiasmata while only occasional bivalents with 6 chiasmata were found. Individuals with sex chromosome anomalies did not differ from individuals with apparently normal karyotypes with regard to distribution of chiasmata per bivalent.

In all patients, except one with a balanced D/D translocation, the autosomes always appeared as typical bivalent structures. Autosomal univalents were not observed at the stages of meiosis examined. As a total of 15, 230 autosome configurations were analysed, these observations indicate a high degree of precision and regularity of pairing and chiasma formation.

The sex chromosomes appeared associated 'end-to-end' in 95.6% of all primary spermatocytes analysed. In 4.4% of the cells the X and Y chromosomes appeared as univalents. This figure is lower than previously reported observations, possibly due to differences in technique.

Individuals with karyotype deviations belonging to the present series were generally found to have an average sperm count of less than 40 million sperms per ml. The majority of patients with chromosomal aberrations, other than the XO/XY and XO/XY/XxO/XxY mosaics, had less than 20 million sperms per ml. All patients with karyotype anomalies had more than 20% morphologically abnormal sperms. The implications of various chromosomal aberrations on gametogenesis of the affected individuals were discussed.

Testicular morphology as well as clinical observations showed no correlation with the different types of chromosome constitution. In the present series, somatic, mental and in particular sexual development did not differ appreciably in the individuals with apparently normal karyotypes as compared to those with different types of chromosome anomalies.

Chromosomal aberrations causing spermatogenetic deficiency and reduced fertility are likely to be recognized only by karyotype analysis of mitotic chromosomes. When indicated such examinations should be supplemented by meiotic chromosome analysis in primary spermatocytes.

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# APPENDIX

*Table A. Cytogenetical, spermatological and clinical data on 135 men attending an infertility clinic*

| Patient | | Cytogenetical data | | | | | | | | | Spermatological data | | | | | Clinical data | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case No. | Tissue cultured | Distribution of chromosome counts | | | | | Total No. of cells counted and analysed | No. of cells photographed and karyotyped | Karyotype interpretation | Sex chromatin in buccal mucosa smears | No. of sperms in millions per ml | | Total No. of ejaculate samples analysed | No. of morphologically abnormal sperms in % | | History of previous conceptions | Duration in years of current period of involuntary childlessness | Age of patient |
| | | 44 | 45 | 46 | 47 | 48 | | | | | range | average | | range | average | | | |
| 1 | B | 1 | 0 | 20 | 0 | 0 | 21 | 3 | 46/XY–N | x | 2– 7 | 5 | 4 | 28–48 | 35 | 0 | 1,5 | 28 |
| | T | 0 | 0 | 22 | 0 | 0 | 22 | 7 | 46/XY–N | | | | | | | | | |
| 2 | B | 1 | 0 | 20 | 0 | 0 | 21 | 4 | 46/XY–N | x | 24– 46 | 32 | 3 | 30– 41 | 36 | 0 | 1 | 29 |
| 3 | B | 0 | 2 | 20 | 0 | 0 | 22 | 3 | 46/XY–N | x | 160–290 | 230 | 4 | 35– 43 | 38 | 0 | 1,5 | 24 |
| 4 | B | 0 | 0 | 22 | 0 | 0 | 22 | 4 | 46/XY–N | x | 40– 59 | 55 | 3 | 30– 42 | 34 | 0 | 2 | 23 |
| 5 | B | 1 | 2 | 15 | 0 | 0 | 18 | 6 | 46/XY–N | x | 133–212 | 182 | 4 | 65– 79 | 68 | 0 | 3 | 31 |
| 6 | BI | 0 | 5 | 30 | 0 | 0 | 35 | 8 | 45/46 | neg. | 20– 64 | 40 | 4 | 32– 57 | 49 | 0 | 12 | 40 |
| | BII | 0 | 2 | 20 | 0 | 0 | 22 | 3 | XO/XY | (–) | | | | | | | | |
| | S | 0 | 3 | 19 | 0 | 0 | 22 | 5 | (mosaicism) | | | | | | | | | |
| 7 | B | 1 | 1 | 20 | 0 | 0 | 22 | 5 | 46/XY–N | x | 89–131 | 111 | 3 | 27– 39 | 33 | 0 | 2 | 25 |
| 8 | B | 1 | 0 | 20 | 1 | 0 | 22 | 3 | 46/XY–N | x | 19– 69 | 38 | 4 | 25– 35 | 30 | 0 | 2 | 36 |
| 9 | B | 0 | 0 | 21 | 0 | 0 | 21 | 4 | 46/XY–N | x | 7– 33 | 20 | 4 | 43– 77 | 66 | 0 | 5 | 31 |
| 10 | B | 0 | 0 | 16 | 0 | 0 | 16 | 4 | 46/XY–N | x | 5– 34 | 18 | 4 | 34– 52 | 43 | ✦ | 3 | 30 |
| 11 | B | 0 | 0 | 22 | 0 | 0 | 22 | 6 | 46/XY–N | x | 96–243 | 143 | 4 | 31– 39 | 34 | **/0 | 2 | 43 |
| 12 | B | 0 | 1 | 15 | 0 | 0 | 16 | 5 | 46/XY–N | x | 19– 31 | 25 | 4 | 23– 35 | 29 | 0 | 5 | 33 |
| | T | 0 | 2 | 17 | 0 | 1 | 20 | 5 | 46/XY–N | | | | | | | | | |
| 13 | B | 0 | 0 | 22 | 0 | 0 | 22 | 4 | 46/XY–N | x | 15– 29 | 24 | 4 | 42– 54 | 47 | 0 | 4 | 33 |
| 14 | B | 0 | 1 | 19 | 0 | 0 | 20 | 3 | 46/XY–N | x | 0– 0 | 0 | 4 | | | 0 | 5 | 25 |
| | T | 0 | 0 | 12 | 0 | 0 | 12 | 2 | 46/XY–N | | | | | | | | | |
| 15 | B | 0 | 0 | 21 | 0 | 0 | 21 | 4 | 46/XY–N | x | 22– 40 | 31 | 4 | 33– 37 | 34 | 0 | 1,5 | 27 |
| 16 | B | 0 | 0 | 18 | 0 | 0 | 18 | 4 | 46/XY–N | x | 25– 83 | 65 | 4 | 28– 43 | 34 | 0 | 0,5 | 38 |
| 17 | B | 0 | 0 | 21 | 0 | 0 | 21 | 3 | 46/XY–N | x | 8– 25 | 16 | 4 | 78–100 | 92 | 0 | 7 | 37 |
| 18 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 44–121 | 75 | 3 | 25– 35 | 27 | 0 | 5 | 25 |
| 19 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 20– 69 | 45 | 4 | 40– 49 | 44 | 0 | 1 | 24 |
| 20 | B | 1 | 0 | 21 | 0 | 0 | 22 | 5 | 46/XY–N | x | 9– 41 | 23 | 4 | 68– 78 | 73 | 0 | 9 | 29 |
| 21 | B | 0 | 1 | 20 | 0 | 0 | 21 | 3 | 46/XY–N | x | 33– 71 | 49 | 4 | 42– 64 | 53 | 0 | 4 | 32 |
| 22 | B | 0 | 0 | 22 | 0 | 0 | 22 | 4 | 46/XY–N | x | 19– 59 | 38 | 4 | 43– 55 | 50 | 0 | 4 | 30 |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 23 | B | 0 | 1 | 22 | 0 | 0 | 23 | 4 | 46/XY–N | x | 17– 48 | 36 | 4 | 23– 41 | 35 | 0 | 6 | 36 |
| 24 | B | 0 | 0 | 22 | 0 | 0 | 22 | 5 | 46/XY–N | x | 0– 0 | 0 | 4 | | | 0 | 6 | 30 |
| 25 | B | 0 | 0 | 11 | 0 | 0 | 11 | 4 | 46/XY–N | x | 5– 28 | 16 | 4 | 18– 75 | 46 | 0 | 10 | 38 |
| | T | 0 | 1 | 19 | 0 | 0 | 20 | 6 | 46/XY–N | x | | | | | | | | |
| 26 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 0– 0 | 0 | 4 | | | *(sic!) | 6 | 31 |
| 27 | B | 0 | 0 | 20 | 1 | 0 | 21 | 3 | 46/XY–N | x | 0– 0 | 0 | 2 | | | 0 | 3 | 31 |
| | T | 0 | 0 | 19 | 0 | 0 | 19 | 3 | 46/XY–N | | | | | | | | | |
| 28 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 24– 46 | 31 | 4 | 40– 73 | 56 | 0 | 3 | 27 |
| | T | 0 | 1 | 19 | 0 | 0 | 20 | 3 | 46/XY–N | | | | | | | | | |
| 29 | B | 0 | 1 | 13 | 1 | 0 | 15 | 5 | 46/XY–N | x | 0– 0 | 0 | 4 | | | 0 | 2 | 27 |
| 30 | B | 0 | 1 | 18 | 0 | 0 | 19 | 4 | 46/XY–N | x | 49– 88 | 61 | 4 | 38– 43 | 42 | 0 | 1 | 26 |
| 31 | B | 0 | 1 | 26 | 0 | 0 | 27 | 7 | 46/XY–N | x | 82–119 | 97 | 4 | 30– 35 | 33 | 0 | 8 | 30 |
| 32 | BI | 0 | 1 | 17 | 1 | 0 | 19 | 6 | 46/XY–N | x | 82–114 | 97 | 4 | 30– 50 | 39 | ✦✦✦ | 5 | 31 |
| | BII | 0 | 0 | 16 | 0 | 0 | 16 | 3 | 46/XY–N | | | | | | | | | |
| 33 | B | 0 | 0 | 12 | 0 | 0 | 12 | 3 | 46/XY–N | x | 433–468 | 448 | 4 | 25– 41 | 33 | 0 | 11 | 41 |
| 34 | B | 1 | 0 | 30 | 0 | 1 | 32 | 7 | 46/XY–N | x | 66–170 | 115 | 4 | 31– 84 | 47 | 0 | 3 | 33 |
| 35 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 39– 82 | 64 | 4 | 16– 40 | 27 | 0 | 8 | 27 |
| 36 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 12– 20 | 16 | 4 | 51– 76 | 64 | 0 | 2 | 24 |
| 37 | B | 0 | 1 | 19 | 0 | 0 | 20 | 4 | 46/XY–N | x | 83– 88 | 86 | 3 | 53– 66 | 59 | * | 9 | 25 |
| 38 | B | 0 | 1 | 19 | 0 | 0 | 20 | 3 | 46/XY–N | x | 5–202 | 117 | 4 | 25– 83 | 43 | * | 3 | 34 |
| 39 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 117–193 | 141 | 4 | 26– 48 | 35 | 0 | 2,5 | 27 |
| 40 | B | 0 | 2 | 26 | 0 | 0 | 28 | 7 | 46/XY–N | x | 0– 0 | 0 | 4 | | | 0 | 1,5 | 28 |
| 41 | B | 0 | 2 | 18 | 0 | 0 | 20 | 3 | 46/XY–N | x | 24– 53 | 39 | 4 | 50– 61 | 56 | 0 | 4 | 48 |
| 42 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | <1–<1 | <1 | 4 | | | 0 | 2 | 29 |
| | T | 0 | 1 | 18 | 0 | 0 | 19 | 3 | 46/XY–N | | | | | | | | | |
| 43 | B | 0 | 1 | 21 | 0 | 0 | 22 | 3 | 46/XY–N | x | 48–123 | 107 | 4 | 36– 54 | 46 | 0 | 1 | 24 |
| 44 | B | 0 | 2 | 18 | 0 | 0 | 20 | 5 | 46/XY–N | x | 42– 86 | 63 | 4 | 31– 42 | 37 | ✦ | 7 | 34 |
| 45 | B | 0 | 0 | 16 | 0 | 0 | 16 | 3 | 46/XY–N | x | 35– 93 | 64 | 4 | 25– 35 | 30 | 0 | 4 | 35 |
| 46 | B | 0 | 1 | 16 | 0 | 0 | 17 | 3 | 46/XY–N | x | 33–156 | 73 | 4 | 32– 40 | 37 | 0 | 2,5 | 25 |
| 47 | B | 0 | 1 | 22 | 0 | 0 | 23 | 3 | 46/XY–N | x | 17–108 | 57 | 4 | 32– 39 | 36 | 0 | 2 | 21 |
| 48 | B | 0 | 0 | 20 | 0 | 0 | 20 | 4 | 46/XY–N | x | 1– 3 | 2 | 4 | 99–100 | 99 | 0 | 2 | 32 |
| | T | 0 | 1 | 15 | 0 | 0 | 16 | 5 | 46/XY–N | | | | | | | | | |
| | S | 1 | 1 | 16 | 0 | 0 | 18 | 3 | 46/XY–N | | | | | | | | | |
| 49 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 56– 91 | 72 | 4 | 32– 49 | 42 | 0 | 2,5 | 27 |
| 50 | B | 0 | 0 | 19 | 0 | 0 | 19 | 3 | 46/XY–N | x | 18– 75 | 46 | 4 | 35– 42 | 38 | 0 | 4 | 50 |

Abbreviations used:
B = peripheral blood
T = testis
S = skin
N = apparently normal male karyotype

x = analysis not performed
pos. = positive
neg. = negative
o = no pregnancy
< = less than

> = more than
✦ = miscarriage
* = normal, living child
/ = signs on any one side of the bar refer to one and the same partner

*Table A* (Continued)

| Patient | | Cytogenetical data | | | | | | | | | Spermatological data | | | | | Clinical data | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case No. | Tissue cultured | Distribution of chromosome counts | | | | | Total No. of cells counted and analysed | No. of cells photographed and karyotyped | Karyotype interpretation | Sex chromatin in buccal mucosa smears | No. of sperms in millions per ml | | Total No. of ejaculate samples analysed | No. of morphologically abnormal sperms in % | | History of previous conceptions | Duration in years of current period of involuntary childlessness | Age of patient |
| | | 44 | 45 | 46 | 47 | 48 | | | | | range | average | | range | average | | | |
| 51 | B | 0 | 2 | 25 | 0 | 0 | 27 | 7 | 46/XY–N | x | 44–110 | 83 | 4 | 29– 36 | 32 | 0 | 3 | 29 |
| 52 | B | 0 | 3 | 18 | 0 | 0 | 21 | 3 | 46/XY–N | x | <1–<1 | <1 | 4 | | | 0 | 4 | 27 |
| 53 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 0– 0 | 0 | 4 | | | 0 | 6 | 27 |
| | T | 0 | 1 | 17 | 0 | 0 | 18 | 3 | 46/XY–N | | | | | | | | | |
| 54 | B | 0 | 1 | 21 | 0 | 0 | 22 | 3 | 46/XY–N | x | 0– 0 | 0 | 4 | | | 0 | 2 | 30 |
| 55 | B | 0 | 8 | 54 | 67 | 2 | 131 | 11 | 46/47– | pos.(+) | 0– 0 | 0 | 4 | | | 0 | 16 | 42 |
| | T | 0 | 1 | 5 | 25 | 0 | 31 | 7 | XY/XXY | | | | | | | | | |
| | S | 0 | 0 | 1 | 29 | 0 | 30 | 5 | (Mosaicism) | | | | | | | | | |
| 56 | B | 0 | 3 | 28 | 2 | 0 | 33 | 7 | 46/XY–N | x | 322–420 | 355 | 4 | 31– 39 | 34 | 0 | 1,5 | 30 |
| 57 | B | 0 | 1 | 18 | 1 | 0 | 20 | 5 | 46/XY–N | x | 49– 81 | 63 | 4 | 26– 41 | 36 | 0 | 5 | 32 |
| 58 | B | 0 | 0 | 19 | 0 | 1 | 20 | 4 | 46/XY–N | x | 24– 84 | 46 | 4 | 29– 47 | 41 | 0 | 4 | 31 |
| 59 | B | 0 | 0 | 16 | 0 | 0 | 16 | 3 | 46/XY–N | x | 27–166 | 84 | 4 | 39– 46 | 44 | ✦✦ | 5 | 35 |
| 60 | T | 0 | 0 | 18 | 0 | 0 | 18 | 3 | 46/XY–N | x | 45–198 | 114 | 4 | 33– 36 | 34 | 0 | 2 | 31 |
| | S | 2 | 2 | 19 | 1 | 0 | 24 | 5 | 46/XY–N | | | | | | | | | |
| 61 | B | 0 | 0 | 17 | 0 | 0 | 17 | 3 | 46/XY–N | x | 0– 0 | 0 | 4 | | | 0 | 2 | 25 |
| 62 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 26–115 | 69 | 4 | 39– 53 | 48 | 0 | 3 | 28 |
| 63 | B | 0 | 0 | 16 | 0 | 0 | 16 | 3 | 46/XY–N | x | 35– 72 | 55 | 4 | 30– 46 | 38 | 0 | 4 | 24 |
| 64 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 33– 90 | 51 | 4 | 25– 41 | 30 | 0 | 5 | 27 |
| 65 | B | 0 | 3 | 22 | 0 | 0 | 25 | 6 | 46/XY–N | x | 13– 16 | 14 | 4 | 65– 72 | 70 | 0 | 8 | 32 |
| 66 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 35–241 | 118 | 4 | 25– 33 | 30 | ✦✦ | 4 | 31 |
| 67 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 57–142 | 91 | 4 | 34– 37 | 36 | 0 | 3 | 24 |
| 68 | B | 0 | 0 | 16 | 0 | 0 | 16 | 3 | 46/XY–N | x | 75– 90 | 84 | 3 | 28– 33 | 30 | 0 | 4 | 38 |
| 69 | B | 0 | 2 | 22 | 0 | 0 | 24 | 5 | 46/XY–N | x | 20– 43 | 32 | 4 | 37– 42 | 39 | 0 | 4 | 31 |
| 70 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 21– 51 | 38 | 4 | 30– 48 | 37 | 0 | 8 | 29 |
| 71 | B | 0 | 0 | 23 | 0 | 0 | 23 | 3 | 46/XY–N | x | 47– 71 | 56 | 3 | 29– 38 | 35 | ✦ | 2 | 27 |
| 72 | B | 0 | 1 | 23 | 0 | 0 | 24 | 3 | 46/XY–N | x | 13– 40 | 29 | 4 | 29– 43 | 36 | ✦ | 2 | 41 |
| 73 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 86–213 | 155 | 4 | 47– 58 | 54 | 0 | 5 | 28 |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 74 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 17– 32 | 26 | 4 | 38– 51 | 43 | 0 | 4 | 74 |
| 75 | BI | 0 | 1 | 35 | 0 | 0 | 36 | 8 | 46/XY–N | x | 29– 58 | 41 | 4 | 20– 34 | 28 | 0 | 4 | 34 |
| | BII | 0 | 1 | 71 | 0 | 0 | 72 | 16 | 46/XY–N | | | | | | | | | |
| | S | 0 | 0 | 30 | 0 | 0 | 30 | 5 | 46/XY–N | | | | | | | | | |
| 76 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 11– 33 | 18 | 4 | 51– 61 | 54 | 0 | 4 | 32 |
| 77 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 6– 20 | 10 | 3 | 23– 57 | 36 | 0 | 5 | 29 |
| 78 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 15– 42 | 26 | 4 | 43– 54 | 48 | 0 | 5 | 28 |
| 79 | BI | 0 | 21 | 28 | 2 | 0 | 51 | 16 | | neg.(—) | 24– 56 | 36 | 4 | 21– 30 | 26 | ✦ | 9 | 30 |
| | BII | 0 | 42 | 53 | 4 | 0 | 99 | 8 | 45/46/47 | | | | | | | | | |
| | TI | 0 | 3 | 34 | 1 | 0 | 38 | 6 | XO/XY/XxO/XxY | | | | | | | | | |
| | TII | 0 | 2 | 12 | 0 | 0 | 14 | 5 | (mosaicism) | | | | | | | | | |
| | S | 0 | 5 | 35 | 0 | 0 | 40 | 6 | | | | | | | | | | |
| 80 | BI | 0 | 10 | 24 | 1 | 0 | 35 | 10 | 45/46 | neg.(—) | 45–119 | 70 | 4 | 24– 38 | 30 | 0 | 5 | 39 |
| | BII | 1 | 10 | 80 | 0 | 1 | 92 | 3 | XO/XY | | | | | | | | | |
| | | | | | | | | | (mosaicism) | | | | | | | | | |
| 81 | B | 0 | 2 | 22 | 0 | 0 | 24 | 3 | 46/XY–N | x | 31– 85 | 63 | 4 | 25– 35 | 29 | * | 5 | 28 |
| 82 | B | 0 | 2 | 22 | 0 | 0 | 24 | 5 | 46/XY–N | x | 23– 38 | 27 | 4 | 35– 41 | 37 | 0 | 1 | 24 |
| 83 | B | 0 | 1 | 19 | 0 | 0 | 20 | 4 | 46/XY–N | x | 5– 13 | 10 | 4 | 33– 36 | 34 | 0 | 2,5 | 29 |
| 84 | B | 0 | 1 | 19 | 0 | 0 | 20 | 4 | 46/XY–N | x | 12– 39 | 25 | 4 | 38– 64 | 48 | 0 | 6 | 38 |
| | T | 0 | 0 | 19 | 0 | 0 | 19 | 3 | 46/XY–N | | | | | | | | | |
| 85 | BI | 0 | 0 | 2 | 40 | 0 | 42 | 14 | 47/XY + extra, | neg. | 0– 0 | 0 | 4 | | | 0 | 3 | 28 |
| | BII | 0 | 1 | 0 | 16 | 0 | 17 | 3 | minute, meta- | (—) | | | | | | | | |
| | S | 0 | 1 | 1 | 18 | 0 | 20 | 5 | centric chromo- | | | | | | | | | |
| | | | | | | | | | some of unknown | | | | | | | | | |
| | | | | | | | | | origin | | | | | | | | | |
| 86 | B | 0 | 1 | 19 | 0 | 0 | 20 | 3 | 46/XY–N | x | 29– 53 | 46 | 4 | 29– 39 | 35 | 0 | 3,5 | 28 |
| 87 | B | 1 | 0 | 20 | 0 | 0 | 21 | 4 | 46/XY–N | x | 11– 38 | 30 | 3 | 21– 33 | 27 | */0 | 5 | 36 |
| 88 | B | 0 | 1 | 20 | 0 | 0 | 21 | 4 | 46/XY–N | x | 129–204 | 163 | 4 | 21– 27 | 23 | 0 | 2 | 33 |
| | T | 0 | 1 | 20 | 0 | 0 | 21 | 3 | 46/XY–N | | | | | | | | | |
| 89 | B | 0 | 0 | 12 | 0 | 0 | 12 | 4 | 46/XY–N | x | 72–244 | 160 | 4 | 19– 34 | 28 | 0 | 3,5 | 31 |
| | T | 0 | 1 | 21 | 0 | 0 | 22 | 4 | 46/XY–N | | | | | | | | | |
| 90 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 78–259 | 200 | 4 | 21– 31 | 26 | 0 | 4,5 | 30 |
| | T | 1 | 0 | 19 | 0 | 0 | 20 | 3 | 46/XY–N | | | | | | | | | |
| 91 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 201–368 | 270 | 3 | 26– 32 | 29 | 0 | 5 | 30 |
| 92 | B | 0 | 0 | 20 | 0 | 0 | 20 | 4 | 46/XY–N | x | 108–178 | 147 | 4 | 16– 46 | 28 | 0 | 11 | 36 |
| | T | 0 | 0 | 11 | 1 | 0 | 12 | 4 | 46/XY–N | | | | | | | | | |
| 93 | B | 0 | 1 | 19 | 0 | 0 | 20 | 3 | 46/XY–N | x | 63–221 | 154 | 4 | 18– 27 | 24 | 0 | 2,5 | 28 |
| 94 | B | 0 | 2 | 36 | 0 | 1 | 39 | 7 | 46/XY–N | x | 97–215 | 144 | 4 | 17– 21 | 20 | 0 | 2 | 33 |
| 95 | B | 0 | 1 | 19 | 0 | 0 | 20 | 3 | 46/XY–N | x | 53– 80 | 63 | 3 | 15– 21 | 19 | 0 | 3 | 30 |
| 96 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 27– 91 | 63 | 4 | 25– 34 | 29 | ✦✦✦ | 3 | 28 |

*Table A* (continued)

| Patient | | Cytogenetical data | | | | | | | | | Spermatological data | | | | | Clinical data | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case No. | Tissue cultured | Distribution of chromosome counts | | | | | Total No. of cells counted and analysed | No. of cells photographed and karyotyped | Karyotype interpretation | Sex chromatin in buccal mucosa smears | No. of sperms in millions per ml | | Total No. of ejaculate samples analysed | No. of morphologically abnormal sperms in % | | History of previous conceptions | Duration in years of current period of involuntary childlessness | Age of patient |
| | | 44 | 45 | 46 | 47 | 48 | | | | | range | average | | range | average | | | |
| 97 | B | 0 | 1 | 19 | 0 | 0 | 20 | 4 | 46/XY–N | x | 119–283 | 210 | 3 | 14– 22 | 18 | ✦✦✦ | 5 | 30 |
| 98 | B | 0 | 2 | 73 | 0 | 0 | 75 | 7 | 46/XY–N | x | 43– 77 | 64 | 4 | 24– 31 | 28 | ✦✦ | 7 | 26 |
| 99 | B | 0 | 2 | 24 | 0 | 0 | 26 | 3 | 46/XY–N | x | 0– 0 | 0 | 4 | | | *(sic!) | 3 | 26 |
| | T | 0 | 2 | 16 | 0 | 0 | 18 | 5 | 46/XY–N | | | | | | | | | |
| | S | 0 | 0 | 18 | 0 | 0 | 18 | 3 | 46/XY–N | | | | | | | | | |
| 100 | B | 0 | 1 | 19 | 0 | 0 | 20 | 3 | 46/XY–N | x | 3– 9 | 4 | 2 | 24– 37 | 33 | 0 | 3 | 34 |
| | T | 0 | 2 | 16 | 0 | 0 | 18 | 4 | 46/XY–N | | | | | | | | | |
| 101 | B | 0 | 0 | 20 | 0 | 0 | 20 | 4 | 46/XY–N | x | 12– 24 | 17 | 4 | 38– 50 | 44 | 0 | 6 | 33 |
| | T | 0 | 1 | 16 | 1 | 0 | 18 | 4 | 46/XY–N | | | | | | | | | |
| 102 | B | 0 | 1 | 20 | 0 | 0 | 21 | 4 | 46/XY–N | x | 0– 0 | 0 | 4 | | | 0 | 8 | 31 |
| | T | 0 | 0 | 61 | 0 | 0 | 61 | 6 | 46/XY–N | | | | | | | | | |
| 103 | T | 0 | 0 | 67 | 1 | 0 | 68 | 7 | 46/XY–N | x | 8– 31 | 16 | 3 | 11– 23 | 19 | */*/0 | 4 | 41 |
| 104 | B | 0 | 0 | 16 | 0 | 0 | 16 | 3 | 46/XY–N | x | 1– 6 | 3 | 4 | 26– 39 | 35 | 0 | 3 | 29 |
| | T | 0 | 0 | 60 | 2 | 0 | 62 | 8 | 46/XY–N | | | | | | | | | |
| 105 | B | 0 | 0 | 13 | 0 | 0 | 13 | 3 | 46/XY–N | x | 3– 7 | 5 | 4 | 37– 43 | 40 | 0 | 4 | 29 |
| | T | 0 | 3 | 34 | 1 | 0 | 38 | 5 | 46/XY–N | | | | | | | | | |
| | S | 0 | 3 | 68 | 1 | 1 | 73 | 7 | 46/XY–N | | | | | | | | | |
| 106 | T | 4 | 2 | 20 | 0 | 0 | 26 | 4 | 46/XY–N | x | 0– 0 | 0 | 4 | | | 0 | 7 | 31 |
| 107 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 0– 0 | 0 | 4 | | | 0 | 4 | 38 |
| | T | 0 | 1 | 60 | 0 | 0 | 61 | 6 | 46/XY–N | | | | | | | | | |
| 108 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/X+ | x | 2– 17 | 9 | 4 | 29– 46 | 35 | 0 | 3 | 33 |
| | TI | 0 | 0 | 17 | 0 | 0 | 17 | 3 | + possibly | | | | | | | | | |
| | TII | 0 | 0 | 45 | 1 | 0 | 46 | 6 | deleted y | | | | | | | | | |
| 109 | B | 4 | 3 | 15 | 0 | 0 | 22 | 6 | 46/XY–N | x | 10– 32 | 22 | 4 | 46– 88 | 63 | 0 | 5 | 32 |
| | T | 0 | 1 | 24 | 0 | 0 | 25 | 4 | 46/XY–N | | | | | | | | | |
| 110 | BI | 1 | 18 | 0 | 0 | 0 | 19 | 7 | | x | 3– 10 | 6 | 4 | 47– 70 | 58 | 0/0 | 2 | 28 |
| | BII | 1 | 14 | 1 | 0 | 0 | 16 | 4 | 45/XY– | | | | | | | | | |

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BIII | 1 | 14 | 0 | 0 | 0 | 15 | 6 | D/D | | | | | | | | | | |
| | T | 0 | 19 | 0 | 0 | 0 | 19 | 5 | translocation | | | | | | | | | | |
| | S | 1 | 20 | 0 | 0 | 0 | 21 | 4 | heterozygote | | | | | | | | | | |
| 111 | B | 0 | 0 | 17 | 1 | 0 | 18 | 3 | 46/XY–N | x | 0– 0 | 0 | 4 | | | 0 | 2 | 26 |
| 112 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 3– 8 | 11 | 3 | 80– 95 | 92 | 0 | 3,5 | 32 |
| 113 | B | 0 | 1 | 20 | 0 | 0 | 21 | 3 | 46/XY–N | x | 0– 0 | 0 | 4 | | | 0 | 6 | 36 |
| 114 | B | 0 | 0 | 19 | 0 | 1 | 20 | 3 | 46/XY–N | x | 2– 7 | 4 | 4 | 47– 74 | 56 | 0 | 2 | 27 |
| | T | 0 | 0 | 13 | 0 | 0 | 13 | 3 | 46/XY–N | | | | | | | | | |
| 115 | B | 1 | 1 | 46 | 4 | 0 | 52 | 16 | 46/47– | neg.(—) | 4– 17 | 10 | 4 | 42– 48 | 46 | 0 | 4,5 | 30 |
| | S | 1 | 2 | 47 | 4 | 0 | 54 | 8 | XY/XXY | | | | | | | | | |
| 116 | B | 3 | 1 | 40 | 0 | 1 | 45 | 22 | 46/XY–N | x | 55– 78 | 69 | 4 | 24– 39 | 33 | 0 | 3 | 36 |
| 117 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 33–123 | 64 | 4 | 33– 76 | 49 | ✦ | 5 | 28 |
| 118 | B | 0 | 0 | 10 | 0 | 0 | 10 | 3 | 46/XY–N | x | 1– 11 | 6 | 4 | 50– 96 | 83 | 0 | 12 | 37 |
| 119 | B | 0 | 0 | 17 | 0 | 0 | 17 | 5 | 46/X + large y | x | 27– 50 | 39 | 3 | 30– 54 | 41 | 0 | 2,5 | 24 |
| 120 | B | 0 | 0 | 0 | 19 | 0 | 19 | 4 | 47/XXY | pos.(+) | 0– 0 | 0 | 4 | | | 0 | 4 | 36 |
| 121 | B | 0 | 1 | 0 | 19 | 0 | 20 | 4 | 47/XXY | pos.(+) | 0– 0 | 0 | 4 | | | 0 | 13 | 36 |
| 122 | B | 0 | 0 | 20 | 0 | 0 | 20 | 5 | 46/XY–N | x | 77–154 | 94 | 4 | 28– 33 | 30 | 0 | 4,5 | 26 |
| | T | 0 | 0 | 16 | 0 | 0 | 16 | 3 | 46/XY–N | | | | | | | | | |
| | S | 1 | 1 | 16 | 0 | 0 | 18 | 5 | 46/XY–N | | | | | | | | | |
| 123 | BI | 0 | 0 | 23 | 54 | 0 | 77 | 8 | 46/47– | pos.(+) | 0– 0 | 0 | 4 | | | 0 | 0,5 | 19 |
| | BII | 0 | 0 | 5 | 20 | 0 | 25 | 3 | XY/XXY | | | | | | | | | |
| | T | 0 | 2 | 9 | 34 | 2 | 47 | 8 | (mosaicism) | | | | | | | | | |
| 124 | B | 1 | 0 | 15 | 0 | 0 | 16 | 3 | 46/XY–N | x | <1–<1 | <1 | 4 | | | 0 | 13 | 36 |
| | T | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | | | | | | | | | |
| | S | 0 | 2 | 6 | 0 | 0 | 8 | 3 | 46/XY–N | | | | | | | | | |
| 125 | B | 1 | 5 | 70 | 2 | 0 | 78 | 8 | 46/XY–N | x | 20–101 | 62 | 4 | 18– 28 | 24 | 0 | 2 | 26 |
| 126 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 57– 86 | 68 | 4 | 16– 28 | 23 | 0 | 5 | 27 |
| 127 | B | 1 | 2 | 19 | 0 | 0 | 22 | 5 | 46/XY–N | x | 0– 0 | 0 | 4 | | | 0 | 4 | 27 |
| 128 | B | 0 | 0 | 11 | 0 | 0 | 11 | 3 | 46/XY–N | x | 61– 77 | 67 | 4 | 36– 44 | 41 | 0 | 8 | 24 |
| 129 | B | 0 | 1 | 19 | 0 | 0 | 20 | 3 | 46/XY–N | x | <1–<1 | <1 | 4 | | | 0 | 3,5 | 30 |
| 130 | B | 0 | 2 | 22 | 0 | 0 | 24 | 3 | 46/XY–N | x | 31– 80 | 59 | 3 | 24– 29 | 27 | ✦ | 4 | 32 |
| 131 | B | 0 | 2 | 23 | 0 | 0 | 25 | 3 | 46/XY–N | x | <1–<1 | <1 | 4 | | | 0 | 3 | 24 |
| 132 | B | 0 | 0 | 20 | 0 | 0 | 20 | 3 | 46/XY–N | x | 12– 40 | 20 | 4 | 47– 63 | 52 | 0 | 2 | 31 |
| 133 | B | 0 | 2 | 21 | 0 | 0 | 23 | 6 | 46/XY–N | x | 59–106 | 83 | 4 | 26– 34 | 29 | 0 | 5 | 35 |
| 134 | B | 0 | 0 | 20 | 0 | 0 | 20 | 4 | 46/XY–N | x | 18– 82 | 37 | 4 | 41– 51 | 46 | ✦✦ | 4 | 30 |
| 135 | B | 0 | 0 | 23 | 0 | 0 | 23 | 3 | 46/XY–N | x | 14– 25 | 18 | 4 | 42– 56 | 49 | 0 | 5 | 36 |

*Table B 1. Meiotic cytogenetical data on 30 men attending an infertility clinic*

| Patient | Complete / Meiotic Chromosome Complement: Distribution of meiotic chromosome element counts together with type of sex chromosome constitution and sex chromosome association | | | | | | | Total No. of cells analysed | No. of cells with apparently complete meiotic chromosome complement | Sex chromosomes: Distribution of variants of sex chromosome constitution and sex chromosome association | | | Autosomes: Distribution of meiotic autosome element counts | | | Interpretation of structure of meiotic autosome elements |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 22 | 23 | | | 24 | | 25 | | | x+y | | xo | 21 | 22 | 23 | |
| Case No. | xy | xy | x‡y | xo | xy | x‡y | x‡y | | | xy | x‡y | | | | | |
| 1 | 3 | 23 | 0 | 0 | 0 | 2 | 0 | 28 | 25 | 23 | 2 | 0 | 0 | 25 | 0 | bivalents |
| 6* | 2 | 16 | 0 | 4 | 0 | 2 | 0 | 24 | 22 | 16 | 2 | 4 | 0 | 22 | 0 | bivalents |
| 12 | 1 | 29 | 0 | 0 | 0 | 1 | 0 | 31 | 30 | 29 | 1 | 0 | 0 | 30 | 0 | bivalents |
| 25 | 4 | 29 | 0 | 0 | 0 | 1 | 0 | 34 | 30 | 29 | 1 | 0 | 0 | 30 | 0 | bivalents |
| 28 | 3 | 28 | 0 | 0 | 0 | 2 | 0 | 33 | 30 | 28 | 2 | 0 | 0 | 30 | 0 | bivalents |
| 29 | 0 | 28 | 0 | 0 | 0 | 0 | 0 | 28 | 28 | 28 | 0 | 0 | 0 | 28 | 0 | bivalents |
| 42 | 1 | 16 | 0 | 0 | 0 | 4 | 0 | 21 | 20 | 16 | 4 | 0 | 0 | 20 | 0 | bivalents |
| 48 | 1 | 14 | 0 | 0 | 0 | 1 | 0 | 16 | 15 | 14 | 1 | 0 | 0 | 15 | 0 | bivalents |
| 60 | 4 | 15 | 0 | 0 | 0 | 0 | 0 | 19 | 15 | 15 | 0 | 0 | 0 | 15 | 0 | bivalents |
| 79* | 0 | 21 | 0 | 9 | 0 | 0 | 0 | 30 | 30 | 21 | 0 | 9 | 0 | 30 | 0 | bivalents |
| 84 | 4 | 13 | 0 | 0 | 0 | 1 | 0 | 18 | 14 | 13 | 1 | 0 | 0 | 14 | 0 | bivalents |
| 87 | 4 | 29 | 0 | 0 | 0 | 0 | 0 | 33 | 29 | 29 | 0 | 0 | 0 | 29 | 0 | bivalents |
| 88 | 3 | 28 | 0 | 0 | 0 | 2 | 0 | 33 | 30 | 28 | 2 | 0 | 0 | 30 | 0 | bivalents |
| 89 | 2 | 16 | 0 | 0 | 0 | 0 | 0 | 18 | 16 | 16 | 0 | 0 | 0 | 16 | 0 | bivalents |
| 90 | 8 | 28 | 0 | 0 | 0 | 2 | 0 | 38 | 30 | 28 | 2 | 0 | 0 | 30 | 0 | bivalents |
| 92 | 2 | 27 | 0 | 0 | 0 | 3 | 0 | 32 | 30 | 27 | 3 | 0 | 0 | 30 | 0 | bivalents |
| 100 | 3 | 16 | 0 | 0 | 0 | 0 | 0 | 19 | 16 | 16 | 0 | 0 | 0 | 16 | 0 | bivalents |
| 101 | 0 | 9 | 0 | 0 | 0 | 0 | 0 | 9 | 9 | 9 | 0 | 0 | 0 | 9 | 0 | bivalents |
| 103 | 2 | 14 | 0 | 0 | 0 | 0 | 0 | 16 | 14 | 14 | 0 | 0 | 0 | 14 | 0 | bivalents |
| 104 | 3 | 22 | 0 | 0 | 0 | 3 | 0 | 28 | 25 | 22 | 3 | 0 | 0 | 25 | 0 | bivalents |
| 105 | 2 | 27 | 0 | 0 | 0 | 0 | 0 | 29 | 27 | 27 | 0 | 0 | 0 | 27 | 0 | bivalents |
| 108* | 6 | 29 | 0 | 0 | 0 | 1 | 0 | 36 | 30 | 29 | 1 | 0 | 0 | 30 | 0 | bivalents |
| 109 | 0 | 13 | 0 | 0 | 0 | 1 | 0 | 14 | 14 | 13 | 1 | 0 | 0 | 14 | 0 | bivalents |
| 110* | 29 | 0 | 1 | 0 | 0 | 0 | 0 | 30 | 30 | 29 | 1 | 0 | 30 | 0 | 0 | + bivalents + trivalent |
| 111 | 2 | 13 | 0 | 0 | 0 | 0 | 0 | 15 | 13 | 13 | 0 | 0 | 0 | 13 | 0 | bivalents |
| 115* | 5 | 28 | 0 | 0 | 0 | 2 | 0 | 35 | 30 | 28 | 2 | 0 | 0 | 30 | 0 | bivalents |
| 116 | 0 | 23 | 0 | 0 | 0 | 0 | 0 | 23 | 23 | 23 | 0 | 0 | 0 | 23 | 0 | bivalents |
| 117 | 8 | 30 | 0 | 0 | 0 | 0 | 0 | 38 | 30 | 30 | 0 | 0 | 0 | 30 | 0 | bivalents |
| 118 | 4 | 30 | 0 | 0 | 0 | 0 | 0 | 34 | 30 | 30 | 0 | 0 | 0 | 30 | 0 | bivalents |
| 122 | 0 | 6 | 0 | 0 | 0 | 1 | 0 | 7 | 7 | 6 | 1 | 0 | 0 | 7 | 0 | bivalents |

X+Y = both sex chromosomes apparently present
XY = the sex chromosomes are linearily conjugated
X‡Y = the sex chromosomes are free
* = aberrant karyotype
XO = the X chromosome is present while the Y chromosome is apparently absent

*Table B 2. Chiasma frequencies and frequency distribution of chiasmata per bivalent in 30 men attending an infertility clinic*

| Patient | Chiasma frequency | | | | | | | Frequency distribution of chiasmata per bivalent | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total No. of cells analysed | Total No. of chiasmata observed per individual | Total No. of terminal chiasmata observed per individual | Number of chiasmata per cell | | Terminalization coefficient | | Total No. of bivalents analysed | Nos. and percentages of bivalents with the following numbers of chiasmata per bivalent | | | | | | | | | | |
| Case No. | | | | range | average | range | average | | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | |
| | | | | | | | | | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| 1 | 25 | 1338 | 876 | 47–59 | 53.5 | 0.56–0.77 | 0.65 | 550 | 3.2 | 14.6 | 8.6 | 39.3 | 7.7 | 35.1 | 2.3 | 10.6 | 0.1 | 0.6 | 0 | 0 |
| 6* | 22 | 1120 | 712 | 44–55 | 50.9 | 0.53–0.86 | 0.64 | 484 | 3.6 | 16.3 | 9.9 | 44.8 | 6.9 | 31.2 | 1.7 | 7.6 | 0 | 0 | 0 | 0 |
| 12 | 30 | 1556 | 1019 | 44–56 | 51.9 | 0.55–0.80 | 0.65 | 660 | 3.6 | 16.2 | 9.3 | 42.4 | 7.0 | 31.8 | 1.9 | 8.5 | 0.2 | 1.1 | 0 | 0 |
| 25 | 30 | 1529 | 1016 | 43–58 | 51.0 | 0.55–0.84 | 0.66 | 660 | 4.0 | 18.1 | 9.6 | 43.5 | 6.2 | 28.3 | 2.0 | 9.1 | 0.2 | 1.1 | 0 | 0 |
| 28 | 30 | 1598 | 1020 | 48–59 | 53.3 | 0.50–0.76 | 0.64 | 660 | 3.2 | 14.4 | 9.3 | 42.1 | 7.2 | 32.7 | 2.1 | 9.6 | 0.3 | 1.2 | 0 | 0 |
| 29 | 28 | 1494 | 952 | 48–58 | 53.4 | 0.54–0.75 | 0.64 | 616 | 3.1 | 14.3 | 8.9 | 40.4 | 7.7 | 34.9 | 2.1 | 9.4 | 0.2 | 0.8 | (0.04) | 0 |
| 42 | 20 | 1001 | 641 | 46–55 | 50.1 | 0.51–0.77 | 0.64 | 440 | 4.7 | 21.4 | 7.9 | 35.9 | 8.1 | 36.6 | 1.4 | 6.1 | 0 | 0 | 0 | 0 |
| 48 | 15 | 830 | 492 | 51–59 | 55.3 | 0.46–0.66 | 0.59 | 330 | 3.7 | 17.0 | 6.5 | 29.7 | 8.6 | 39.1 | 2.9 | 13.3 | 0.2 | 0.9 | 0 | 0 |
| 60 | 15 | 812 | 538 | 50–62 | 54.1 | 0.57–0.75 | 0.66 | 330 | 3.7 | 16.7 | 7.2 | 32.7 | 8.7 | 39.7 | 2.1 | 9.7 | 0.3 | 1.2 | 0 | 0 |
| 79* | 30 | 1588 | 959 | 44–59 | 52.9 | 0.38–0.73 | 0.60 | 660 | 3.5 | 16.1 | 8.6 | 39.2 | 7.3 | 33.2 | 2.4 | 11.1 | 0.1 | 0.5 | 0 | 0 |
| 84 | 14 | 717 | 483 | 44–57 | 51.2 | 0.49–0.82 | 0.67 | 308 | 3.1 | 14.3 | 10.5 | 14.7 | 6.5 | 29.6 | 1.7 | 7.8 | 0.1 | 0.6 | 0 | 0 |
| 87 | 29 | 1518 | 961 | 47–59 | 52.3 | 0.55–0.77 | 0.63 | 638 | 3.7 | 16.9 | 8.8 | 39.8 | 7.1 | 32.3 | 2.3 | 10.4 | 0.1 | 0.6 | 0 | 0 |
| 88 | 30 | 1557 | 975 | 46–58 | 51.9 | 0.51–0.77 | 0.63 | 660 | 3.4 | 15.6 | 9.1 | 41.4 | 7.7 | 35.0 | 1.7 | 7.6 | 0.1 | 0.5 | 0 | 0 |
| 89 | 16 | 837 | 541 | 47–57 | 52.3 | 0.51–0.79 | 0.65 | 352 | 3.5 | 15.9 | 9.4 | 42.6 | 6.9 | 31.3 | 1.9 | 8.6 | 0.3 | 1.4 | 0.1 | 0.3 |
| 90 | 30 | 1650 | 1035 | 47–64 | 55.0 | 0.41–0.76 | 0.63 | 660 | 3.8 | 17.3 | 7.4 | 33.5 | 7.5 | 34.0 | 2.8 | 12.7 | 0.5 | 2.4 | (0.03) | 0.1 |
| 92 | 30 | 1612 | 989 | 48–58 | 53.7 | 0.47–0.76 | 0.61 | 660 | 3.1 | 14.2 | 9.1 | 41.2 | 7.0 | 32.0 | 2.5 | 11.2 | 0.3 | 1.4 | 0 | 0 |
| 100 | 16 | 802 | 498 | 44–58 | 50.1 | 0.48–0.78 | 0.62 | 352 | 3.6 | 16.2 | 10.7 | 48.6 | 6.1 | 27.6 | 1.4 | 6.6 | 0.3 | 1.1 | 0 | 0 |
| 101 | 9 | 457 | 283 | 43–57 | 50.8 | 0.49–0.69 | 0.62 | 198 | 4.3 | 19.7 | 8.3 | 37.9 | 7.6 | 34.4 | 1.8 | 8.1 | 0 | 0 | 0 | 0 |
| 103 | 14 | 724 | 503 | 47–57 | 51.7 | 0.58–0.79 | 0.69 | 308 | 3.7 | 16.9 | 8.9 | 40.6 | 7.4 | 33.8 | 1.8 | 8.1 | 0.1 | 0.6 | 0 | 0 |
| 104 | 25 | 1343 | 815 | 45–61 | 53.7 | 0.47–0.76 | 0.61 | 550 | 3.6 | 16.4 | 8.0 | 36.6 | 7.6 | 34.7 | 2.5 | 11.3 | 0.2 | 1.1 | 0 | 0 |
| 105 | 27 | 1453 | 935 | 48–59 | 53.8 | 0.50–0.79 | 0.64 | 594 | 3.1 | 14.1 | 8.9 | 40.2 | 7.4 | 33.7 | 2.4 | 10.8 | 0.3 | 1.2 | 0 | 0 |
| 108* | 30 | 1531 | 1042 | 46–57 | 51.0 | 0.58–0.80 | 0.68 | 660 | 3.8 | 17.4 | 9.6 | 43.8 | 6.3 | 28.6 | 2.1 | 9.7 | 0.1 | 0.5 | 0 | 0 |
| 109 | 14 | 754 | 506 | 49–59 | 53.9 | 0.56–0.75 | 0.67 | 308 | 3.5 | 15.9 | 8.4 | 38.3 | 7.1 | 32.5 | 2.6 | 11.7 | 0.4 | 1.6 | 0 | 0 |
| 110* | 30 | 1411 | 890 | 39–54 | 47.0 | 0.46–0.69 | 0.63 | — | | — | | — | | — | | — | | — | | — |
| 111 | 13 | 680 | 426 | 50–55 | 52.3 | 0.48–0.71 | 0.63 | 286 | 3.9 | 17.5 | 8.6 | 39.2 | 7.3 | 33.2 | 1.9 | 8.7 | 0.2 | 1.1 | 0.1 | 0.4 |
| 115* | 30 | 1598 | 1040 | 49–59 | 53.3 | 0.54–0.76 | 0.65 | 660 | 3.7 | 16.7 | 8.6 | 39.2 | 6.9 | 31.2 | 2.4 | 11.1 | 0.4 | 1.8 | 0 | 0 |
| 116 | 23 | 1179 | 812 | 46–57 | 51.2 | 0.58–0.85 | 0.69 | 506 | 3.7 | 17.0 | 9.3 | 42.1 | 7.1 | 32.2 | 1.8 | 8.3 | 0.1 | 0.4 | 0 | 0 |
| 117 | 30 | 1589 | 1009 | 47–61 | 53.0 | 0.49–0.78 | 0.64 | 660 | 3.7 | 16.8 | 8.1 | 36.8 | 8.0 | 36.5 | 1.9 | 8.6 | 0.2 | 1.1 | (0.03) | 0.1 |
| 118 | 30 | 1577 | 1005 | 43–60 | 52.6 | 0.41–0.88 | 0.64 | 660 | 3.6 | 16.4 | 9.0 | 40.8 | 6.9 | 31.4 | 2.3 | 10.6 | 0.2 | 0.9 | 0 | 0 |
| 122 | 7 | 384 | 240 | 48–58 | 54.9 | 0.54–0.79 | 0.63 | 154 | 3.4 | 15.6 | 7.3 | 33.1 | 8.4 | 38.3 | 2.7 | 12.3 | 0.1 | 0.6 | 0 | 0 |

* = aberrant karyotype

*Table C. Testicular morphology in 47 men attending an infertility clinic*

spg = spermatogonium, I spc = primary spermatocyte, spt = spermatid, spz = sperm (spermatozoa)

| Case No. | Germinal epithelium | | Sertoli cells | Seminiferous tubules | | Interstitial cells | | Histo-pathological diagnosis | Age of pat. | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cell stages present | Spermatogenetic activity | | Size | Thickness of the walls | Relative number | Predominating type of cells | | | |
| 1 | spg-spz | Appar. normal in reduced No. of sem. tubules | Appar. normal in reduced No. of sem. tubules | From appar. normal, post puber. type to obliterated 'ghost' tubules. Extensive reduct. in No. | From appar. normal to extensive sclerosis ('ghost' tubules) in addition to peritubular fibrosis | Moderately increased | Fibrocyte-like | Testicular morphology consistent with state after infection | 28 | Severe mumps-orchitis at the age of 21 |
| 6 | spg-spz | Appar. normal | Appar. normal, | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Appar. normal testicular morphology | 40 | |
| 12 | spg-spz | Slight reduct. in relative No. of spt-spz. Earlier stages appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Testicular morphology consistent with slight partial intratubular spermatogenetic arrest at the I spc level | 33 | |
| 14 | 0 | 0 | Appar. normal | Slight reduct. of diam. A few tubules of puber. type | From appar. normal to moderately increased with sclerosis and peritubular fibrosis | Moderately increased | Fibrocyte-like | Germinal cell aplasia | 25 | |
| 25 | spg-spz | Slightly reduced | Appar. normal | Appar. normal, post puber. type | Appar. normal | Slightly increased | Leydig | Testicular morphology consistent with slight impairment of spermatogenetic activity in general | 38 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 27 | 0 | 0 | Appar. normal | Slight reduct. of diam., post puber. type | From appar. normal to moderately peritubular fibrosis in a few tubules | Fibrous tissue elements increased | Fibro-cyte-like | Germinal cell aplasia with peritubular and interstitial fibrosis | 31 | |
| 28 | spg-spz | Appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Appar. normal testicular morphology | 27 | |
| 29 | spg-spz | Appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Appar. normal testicular morphology | 27 | No history of previous infections, includ. vener. diseases or injuries to the reproductive organs which by clinical examination seem to be morphologically normal (Aspermia) |
| 40 | 0 | 0 | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Germinal cell aplasia | 28 | |
| 42 | spg-spz | Obvious reduct. in relative No. of spermatids and spermato-zoas. Earlier stages including metaphase I appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Testicular morphology consistent with partial intratubular spermato-genetic arrest at the I spc (metaphase I) level | 29 | |
| 48 | spg-spz | Obvious reduct. in relative No. of spz. Earlier stages, including spt stage, appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Testicular morphology consistent with partial intratubular spermato-genetic arrest at the spt-level | 32 | |
| 53 | 0 | 0 | Appar. normal | Average diam. slightly reduced. Puber. and post puber. types | Appar. normal | Appar. normal | Mixed | Germinal cell aplasia | 27 | |

*Table C* (Continued)

| Case No. | Germinal epithelium | | Sertoli cells | Seminiferous tubules | | Interstitial cells | | Histo-pathological diagnosis | Age of pat. | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cell stages present | Spermatogenetic activity | | Size | Thickness of the walls | Relative number | Predominating type of cells | | | |
| 55 | 0 | 0 | Severely reduced in No., in only a few patent tubules | From a few patent, but size reduced tubules to a majority of completely obliterated 'ghost'-tubules. Puber. type | Markedly increased, hyalinization and sclerosis. 'Ghost'-tubules prevailing | Increased | Leydig | Testicular morphology consistent with the findings in Klinefelter's syndrome | 42 | |
| 60 | spg-spz | Appar. normal | Appar. normal | Appar. normal, post puber. type | Most tubules appar. normal. A few tubules hyalinized | Appar. normal | Mixed | Appar. normal testicular morphology | 31 | |
| 79 | spg-spz | Appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Leydig | Appar. normal testicular morphology | 30 | |
| 84 | spg-spz | Appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Appar. normal testicular morphology | 38 | |
| 85 left testicle | 0 | 0 | Appar. normal | Moderately reduced in diam., pre-puber. and puber. type | Slightly increased; hyalinisation but no obvious sclerosis or peritubular fibrosis | Slightly increased | Leydig | Germinal cell aplasia | 28 | Orchidopexy at the age of 26 for unilateral undescended testicle |
| right testicle | 0 | 0 | Appar. normal | Slightly reduced in diam., post puber. type | Appar. normal | Appar. normal | Mixed | Germinal cell aplasia | | No testicular retention |
| 87 | spg-spz | Appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Appar. normal testicular morphology | 36 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 88 | spg-spz | Appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Appar. normal testicular morphology | 33 | |
| 89 | spg-spz | Appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Appar. normal testicular morphology | 31 | |
| 90 | spg-spz | Appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Appar. normal testicular morphology | 30 | |
| 92 | spg-spz | Appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Appar. normal testicular morphology | 36 | |
| 99 | spg | 0 | Appar. normal | Appar. normal, post puber. type | Appar. normal | Slightly increased | Fibro-cyte-like | Testicular morphology consistent with severe reduction of germinal epithelium in general. Complete spermato-genetic arrest at the spg-level | 26 | Always perfectly healthy until Nov. 1961. In late Oct. 1961 the patient's wife became pregnant and a normal, healthy girl was born after an uneventful pregnancy. In Nov. 1961 there was a sudden, unexplained onset of Diabet. insipidus. Two months later complete lack of libido and inability to perform marital intercourse. Subsequently, moderate decrease in size of testicles but other reproductive organs normal clinically. Pitressin-therapy controlled the Diabetes insipidus, and no other therapy has been recommended as yet. |

*Table C* (Continued)

| Case No. | Germinal epithelium | | Sertoli cells | Seminiferous tubules | | Interstitial cells | | Histo-pathological diagnosis | Age of pat. | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cell stages present | Spermatogenetic activity | | Size | Thickness of the walls | Relative number | Predominating type of cells | | | |
| 100 | spg-spz | Appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Appar. normal testicular morphology | 34 | |
| 101 | spg-spz | Moderately reduced | Appar. normal | From appar. normal to obliterated; post puber. type | From appar. normal to moderately increased; and hyalinised together with slight peritubular fibrosis | Slightly increased | Fibrocyte-like | Testicular morphology consistent with moderate tubular sclerosis and moderately impaired spermatogenetic activity in general | 33 | |
| 103 | spg-spz | Appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Appar. normal testicular morphology | 41 | |
| 104 | spg-spz | Appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Appar. normal testicular morphology | 29 | |
| 105 | spg-spz | Appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Appar. normal testicular morphology | 29 | |
| 106 | 0 | 0 | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Germinal cell aplasia | 31 | |
| 107 | spg? | 0 | Extensive reduct. in No. Many degenerated forms | From occasionally appar. normal to obliterated 'ghost' tubules | Severely increased with extensive hyalinisation and sclerosis | Slightly increased | Fibrocyte-like | Testicular morphology consistent with severe tubular sclerosis with complete absence of spermatogenesis | 38 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 108 left testicle | spg-spz | Obvious reduct. in relative No. of late spt and spz. Earlier stages includ. early spt, appar. normal | Appar. normal | From appar. normal to occasionally obliterated 'ghost' tubules post puber. type | Moderately increased with sclerosis and peritubular fibrosis | Slightly increased | Mixed | Testicular morphology consistent with moderate tubular sclerosis and partial intratubular spermatogenetic arrest at the spt level | 33 | |
| right testicle | spg-spz | Obvious reduct. of the germinal epithelium in general. Very few spt and spz | Appar. normal in persistent not obliterated tubules | From appar. normal to obliterated 'ghost' tubules; prepuber. to puber. type | Moderately to severely increased with sclerosis and peritubular fibrosis | Increased | Leydig | Testicular morphology consistent with severe tubular sclerosis and peritubular fibrosis and with severely reduced spermatogenetic activity in tubules of the prepuber. and puber. type | | Orchidopexy at the age of 22 for unilateral undescended testicle |
| 109 | spg-spz | Appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Appar. normal testicular morphology | 32 | |
| 110 | spg-spz | Moderate reduct. in relative No. of late spt-spz. Earlier stages up to the early spt level appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Testicular morphology consistent with partial intratubular spermatogenetic arrest at the spt level | 28 | |
| 111 | spg-spz | Slightly increased relative No. of spt-spz | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Appart. normal testicular morphology with slightly increased relative No. of spermatids and spermatozoas | 26 | Psycho-sexual aberration in the form of masochism-fetishism. No history of previous disease or injury. X-ray examination revealed no obstruction in the vasa defer. Congenit. malformation of caput epidid.? (Aspermia) |

*Table C* (Continued)

| Case No. | Germinal epithelium: Cell stages present | Germinal epithelium: Spermatogenetic activity | Sertoli cells | Seminiferous tubules: Size | Seminiferous tubules: Thickness of the walls | Interstitial cells: Relative number | Interstitial cells: Predominating type of cells | Histo-pathological diagnosis | Age of pat. | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| 112 | spg-spz | Moderately impaired in general. Relative No. of spt-spz obviously reduced | Appar. normal in most non-obliterated tubules | From appar. normal to 'ghost' tubules | Moderately increased; hyalinisation and sclerosis; mild peri-tubular fibrosis | Appar. normal | Mixed | Testicular morphology consistent with slight to moderate tubular sclerosis and peritubular fibrosis in addition to partial intratubular spermatogenetic arrest at the I spc (meta-phase I) level | 32 | |
| 113 | 0 | 0 | Appar. normal | Appar. normal, post puber. type | Appar. normal | Slightly increased | Leydig | Germinal cell aplasia | 36 | |
| 114 | spg-spz | Mainly appar. normal. Locally increased No. of degenerating cells | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Appar. normal testicular morphology with a slight increase locally in No. of degenerating germinal cells | 27 | |
| 115 | spg-spz | Appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Appar. normal testicular morphology | 30 | |
| 116 | spg-spz | Appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Appar. normal testicular morphology | 36 | |
| 117 | spg-spz | Appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Appar. normal testicular morphology | 28 | |
| 118 | spg-spz | Locally slightly reduced | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Appar. normal testicular morphology | 37 | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 119 | spg-spz | Moderate reduct. of relative No. of spz. Earlier stages up to spt level appar. normal | Appar. normal | Appar. normal, post puber. type | Appar. normal | Appar. normal | Mixed | Testicular morphology consistent with partial spermatogenetic arrest at the spt level | 24 |
| 120 | 0 | 0 | Severely reduced and only present in a few non-obliterated tubules | From a few patent but size reduced to completely obliterated 'ghost' tubules | Markedly increased; hyalinisation and sclerosis. 'Ghost' tubules prevailing | Increased | Leydig | Testicular morphology consistent with the findings in Klinefelter's syndrome | 36 |
| 121 | 0 | 0 | Severely reduced and only present in a few non-obliterated tubules | From a few patent but size reduced to completely obliterated 'ghost' tubules | Markedly increased; hyalinisation and sclerosis. 'Ghost' tubules prevailing | Increased | Leydig | Testicular morphology consistent with the findings in Klinefelter's syndrome | 36 |
| 122 | spg-spz | Appar. normal | Appar. normal | Appar. normal | Appar. normal | Slightly increased | Fibro-cyte-like | Appar. normal testicular morphology | 26 |
| 123 | 0 | 0 | Severely reduced and only present in a few non-obliterated tubules | From a few patent but size reduced to completely obliterated 'ghost' tubules | Markedly increased; hyalinisation and sclerosis. 'Ghost' tubules prevailing | Increased | Mixed | Testicular morphology consistent with the findings in Klinefelter's syndrome | 19 |
| 124 | spg-I-spc in 1st meiotic prophase (pachy-tene) | Severely impaired. Intratubular spermatogenetic arrest at the I spc (pachytene) level. Increased No. of degenerating cells | Appar. normal | Mean diam. slightly reduced; post puber. type | Slightly increased; moderate hyalinisation but no obvious sclerosis or peritubular fibrosis | Slightly increased | Leydig | Testicular morphology consistent with severe intratubular spermatogenetic arrest at the I spc level | 36 |

*Table D. Relevant features in the history and clinical data of 12 men with apparently aberrant karyotypes attending an infertility clinic*

| Patient | | | Family data | | | | Sexual development and history | | | | | | | Clinical data | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case No. | Age of pat. | Karyotype interpretation | No. in sibship | Age of mother at pat's birth | Age of father at pat's birth | Family history, incl. karyotypes of relatives | Childhood development | Age at onset of puberty | Age at 1st intercourse | No. of premarital partners | Age at marriage | Present a) libido and b) coital competence | Frequency of marital intercourse | Previous medical history: Diagnosis/age | Body proportions | Height/Span in cm | Weight in kg | Secondary sex characteristics | Shaving frequency | Size of testes in mm L = left R = right | Prostate | Penis |
| 120 | 36 | 47/XXY | 4/4 | 37 | 45 | — | Normal | 15 | ? | 2 | 32 | Good | Once weekly | Mumps (no orchit.) / 14<br>Mild anemia / 34<br>Orthostatic hypotension | Leptosome, somewhat eunuchoid | 189/193 | 66 | Normal, no gynecomastia | Twice weekly | L = small, soft<br>R = small, soft | Normal | Normal |
| 121 | 36 | 47/XXY | 15/15 | 49,5 | 53 | 1 brother and 2 maternal uncles mentally defective | Delayed | 16 | 27 | 1 | 31 | a) weak but<br>b) satisfactory<br>Small ejaculate | Once in 3 weeks | Slight mental retardation<br>Muscular weakness | Female | 178/184 | 87 | Gynecomastia<br>Female escatcheon<br>High-pitched voice<br>Scanty axillary and pub. hair | Once monthly | L = 23×13 mm<br>R = 26×13 mm | Small | Small |
| 115 | 30 | 46/47<br>XY/XXY | 1/3 | 28 | 27 | — | Normal | 14 | 18 | 2 | 24 | a) fair<br>b) satisfactory | Once in 2 weeks | Mumps / 5 | Normal | 176/177 | 75 | Normal | Daily | L = 43×29 mm<br>R = 40×27 mm | Normal | Normal |
| 123* | 19 | 46/47<br>XY/XXY | 3/4 | ? | 30 | — | Normal | 13 | — | 0 | — | a) weak<br>b) none | — | — | Leptosome | 202/196 | 79 | Male escatcheon<br>Scanty axillary and pub. hair | Less than once weekly | L = 25×12 mm<br>R = 25×12 mm | Normal | Normal |
| 55 | 42 | 46/47<br>XY/XXY | 5/8 | 31 | 52 | Brothers (2) involuntary childless. All sisters have children | Normal | 14 | 16 | 4 | 26 | a) good<br>b) satisfactory | Once weekly | — | Somewhat eunuchoid | 179/181 | 82 | Normal, high pitched voice | Twice weekly | L = 26×16 mm<br>R = 24×16 mm | Normal | Normal |
| 79 | 30 | 45/46/47<br>XO/XY/XxO/XxY | 5/5 | 45 | 47 | — | Normal | 14 | 19 | 2 | 20 | a) good<br>b) satisfactory | 3 times weekly | — | Normal | 172/169 | 75 | Normal | Daily | L = 45×26 mm<br>R = 43×25 mm | Normal | Normal |
| 6 | 40 | 45/46<br>XO/XY | 1/2 | 30 | 31 | — | Normal | 14 | 25 | 0 | 27 | a) good<br>b) satisfactory | 3 times weekly | Rickets? / 2–5?<br>Mild prostatitis / 33 | Leptosome | 190/190 | 70 | Normal | Daily | L = 43×30 mm<br>R = 42×27 mm | Normal | Normal |
| 80 | 39 | 45/46<br>XO/XY | 1/1 | 20 | 28 | — | Normal | 13 | 19 | 0 | 34 | a) good<br>b) satisfactory | Twice weekly | — | Normal | 179/180 | 72 | Normal | Daily | L = 40×30 mm<br>R = 39×28 mm | Normal | Normal |
| 85 | 28 | 47/XY+extra, minute, -meta-centric chromosome of unknown origin | 3/3 | 41 | 50 | One brother involuntary childless. Mothers karyotype: 46/XX-normal | Normal | 14 | 19 | 5 | — | a) good<br>b) satisfactory | 3–4 times weekly | Left orchidopexy / 26 | Normal | 175/175 | 71 | Normal | Daily | L = small, soft<br>R = 40×23 mm | Normal | Normal |
| 110 | 28 | 45/XY<br>T: D/D | 3/3 | 22 | 39 | Karyotypes of:<br>Mother: 46/XX-norm.<br>Brother: 46/XY-norm.<br>Father and 1 brother died of TB | Normal | 14 | 17 | 2 | I 25<br>II 27 | a) good<br>b) satisfactory | 3 times weekly | Poliomyelitis / 12<br>(no residua)<br>Severe gastritis / 21<br>Pulmonary tuberculosis (quiescent) / 25 | Leptosome | 179/178 | 60 | Normal | Daily | L = 35×23 mm<br>R = 32×23 mm | Normal | Normal |
| 108 | 33 | 46/Xy<br>Very small Y-chromosome | 1/1 | 32 | 34 | Father deceased. Pat's uncle involuntary childless and with a similar small Y-chromosome in his complement | Hypospadias, otherwise normal | 15 | 19 | 1 | 29 | a) good<br>b) satisfactory after surgical correction of hypospadias | Once weekly | Mumps (no orchit.) / 10<br>Mild stenosis of infundib. part of pulm. arter. diagnosed at the age of 22<br>Surgical correction of hypospadias and right orchidopexy / 23 | Normal | 172/169 | 75 | Normal | Daily | L = 40×28 mm<br>R = small, soft | Normal | Surgically corrected hypo-spadias |
| 119 | 24 | 46/XY<br>Very large Y-chromosome | 3/3 | 35 | 48 | — | Normal | 14 | 16 | 1 | 20 | a) weak<br>b) satisfactory | Once in 2 months | — | Leptosome<br>Somewhat eunuchoid | 186/198 | 71 | Normal | Once in 2 days | L = 43×30 mm<br>R = 44×32 mm | Normal | Normal |

* The details of this pat. will be published by Annell *et al.* (in prep.)

¾ = the third child in a sibship of four